**IN THE UNITED STATES DISTRICT COURT**

**FOR THE DISTRICT OF DELAWARE**

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| MEDPOINTE HEALTHCARE INC., Plaintiff, v. APOTEX INC. AND APOTEX CORP., Defendants. | C. A. No. 06-164-SLR **REDACTED PUBLIC VERSION** |

**MEDPOINTE'S RESPONSE BRIEF ON CLAIM CONSTRUCTION ISSUES**

Frederick L. Cottrell, III (#2555)
cottrell@rlf.com
Kelly E. Farnan (#4395)
farnan@rlf.com
RICHARDS, LAYTON & FINGER P.A.
One Rodney Square
P.O. Box 551
Wilmington, Delaware 19899
(302) 651-7700

*Attorneys for Plaintiff MedPointe Healthcare Inc.*

*Of Counsel:*

John M. Desmarais
Peter J. Armenio
Anne S. Toker
KIRKLAND & ELLIS LLP
Citigroup Center
153 East 53rd Street
New York, New York 10022
(212) 446-4800

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## INTRODUCTION

Pursuant to the Court's June 5, 2007 Amended Rule 16 Scheduling Order (D.I. 85), Plaintiff MedPointe Healthcare Inc. ("MedPointe") respectfully submits this response brief in further support of its proposed claim constructions.

The patent-in-suit, U.S. Patent No. 5,164,194 ("the '194 patent"), claims novel methods of treating irritation or disorders of the nose and eye by applying the compound azelastine directly to nasal tissues or the conjunctival sac of the eyes. As set forth in its opening brief (D.I. 105), MedPointe proposes constructions for the disputed claim terms that follow their plain and ordinary meanings, the specification and the prosecution history. MedPointe's proposed constructions are further supported by the testimony of experts for both parties.

Apotex, by contrast, proposes out-of-context definitions that bear no relation to the specification of the '194 patent or other intrinsic evidence. The Federal Circuit has rejected Apotex's *ad hoc* approach to claim construction. This Court should do the same.

Unable to support its proposed claim constructions with appropriate evidence under *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*), Apotex instead attacks the presumptive validity of the '194 patent. (Apotex Op. Br. at 1). But these arguments are premature and irrelevant to the Court's claim construction analysis. They are also flat wrong. At trial, Apotex will be unable to meet its burden of proving invalidity by clear and convincing evidence because, *inter alia*: (1) persons of ordinary skill in the art would not have attempted to formulate azelastine as a nasal spray in light of its exceptionally bitter taste; (2) persons of ordinary skill would not have attempted to formulate an azelastine nasal spray in light of the widely held belief that topical application of antihistamines was unsafe and ineffective; and (3) Astelin®, a commercial embodiment of the patent-in-suit that Apotex seeks to copy, has been a

commercial success that, despite others' efforts, remains the only antihistamine nasal spray approved by the United States Food and Drug Administration.

For all the reasons set forth herein and in its opening claim construction brief, MedPointe respectfully requests that the Court adopt MedPointe's proposed constructions of the disputed claim terms.

## NATURE AND STAGE OF THE PROCEEDINGS

In accordance with the Court's June 5, 2007 Amended Rule 16 Scheduling Order (D.I. 85), the parties submitted their simultaneous opening briefs on claim construction issues (D.I. 102, 105) on December 17, 2007. MedPointe subsequently informed Apotex that, because the Apotex product infringes the '194 patent under both MedPointe's and Apotex's proposed constructions, it would be inappropriate for Apotex to seek a trial on infringement issues. In response, Apotex agreed to stipulate to infringement of Claims 4, 5, 7, 8 and 9 of the '194 patent and the parties are currently negotiating the precise wording of a proposed consent order to submit for the Court's consideration.

## SUMMARY OF THE ARGUMENT

For each of the disputed claim terms, MedPointe proposes a construction that relies on the plain and ordinary meaning of the claim term as it would be understood by a person of ordinary skill in the art. MedPointe's proposed constructions are consistent with the '194 patent specification and the patentee's statements in the prosecution history, as required by the Federal Circuit's decision in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*). Expert testimony – by experts for both parties – further supports MedPointe's proposed constructions.

Apotex, by contrast, proposes constructions that bear no relation to the invention disclosed in the '194 patent. Apotex seeks to construe claim terms in a vacuum to suit its

litigation objectives, rather than in the context of the specification as *Phillips* requires. As the Federal Circuit has emphasized, "claims are not construed in a vacuum, but rather in the context of the intrinsic evidence, *viz.*, the other claims, the specification, and the prosecution history." *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003).

For example, Apotex's proposed construction of the term "a medicament" does not require the presence of an active ingredient, even though providing such an active ingredient, azelastine, is a fundamental point of the '194 patent specification. Indeed, providing an active ingredient, medicine, is what makes a substance a medicament. Apotex overlooks this key fact and many others in its haste to promote results-oriented constructions divorced from the intrinsic evidence.

After considering the intrinsic and extrinsic evidence discussed in detail below, MedPointe respectfully requests that the Court adopt its proposed constructions as set forth in Exhibit 1.

## ARGUMENT

### I. THE APPLICABLE LEGAL STANDARDS

The Court is well aware of the applicable legal standards for claim construction issues, which MedPointe summarized for the Court's convenience in its opening brief. In this brief, MedPointe summarizes the law on the use of preamble language in claim construction since Apotex seeks to remove such language from the claim construction process.

The preamble of a claim may limit its scope. As the Federal Circuit has explained:

> "***If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim***. . . . If, however, the body of the claim fully and intrinsically sets forth the complete invention, including all of its

> limitations, and the preamble offers no distinct definition of any of the claimed invention's limitations, but rather merely states, for example, the purpose or intended use of the invention, then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation."

*Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (internal citations omitted) (emphases added). "[W]hen the claim drafter chooses to use both the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects." *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003).

## II. MEDPOINTE'S PROPOSED CLAIM CONSTRUCTIONS

### A. "Irritation Or Disorders Of The Nose And Eye"

As set forth in MedPointe's opening brief, the phrase "irritation or disorders of the nose and eye" should be construed to mean "Rhinitis and/or conjunctivitis, including seasonal allergic rhinitis and vasomotor rhinitis. Symptoms of rhinitis include itching (also known as "pruritus"), sneezing, increased secretions (also known as "rhinorrea"), and congestion." MedPointe's proposed construction is supported by the plain and ordinary meaning, the specification and the prosecution history.

Rhinitis and/or conjunctivitis — inflammation of the nasal mucous membrane and/or conjunctiva — are the ***only*** types of irritations or disorders of the nose and eye that the specification and prosecution history contemplate or disclose. As explained in detail in MedPointe's opening brief, ***every*** irritation or disorder that the specification discloses (*e.g.*, common cold, allergic blepharoedema, catarrhal conditions in the eye or nose, coryza) is a type of rhinitis and/or conjunctivitis. *See, e.g.*, Ex. 2, col 1, ll. 40-43; 50-52.

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(MedPointe Op. Br. at 6-8.)

Apotex argues that the Claim 1 preamble does not limit that claim or the asserted claims that depend from it. But this argument is meritless. The phrase "for the treatment of irritations or disorders of the nose and eye" as incorporated into dependent Claims 4, 5, 7, 8 and 9 of the '194 patent is limiting because it is necessary to give "life, meaning, and vitality" to the claims. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). In particular, the claim preamble specifies that azelastine is intended to act in the nose and eye to treat disorders of the nose and eye.

In *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003), cited by Apotex, the Federal Circuit held that a preamble was limiting if it specified "the intentional purpose for which the method must be performed." In *Jansen*, the preamble specified that the method was a method "of treating or preventing macrocytic-megaloblastic anemia in humans." *Jansen*, 342 F.3d at 1330. The court found that this preamble was "not merely a statement of effect that may or may not be desired or appreciated" and that the inventor had "limited his claims to treatment or prevention of that particular condition in those who need such treatment or prevention." *Id.* at 1333-34. The court held that administering the claimed treatment in the claimed doses for a purpose other than treatment of the particular disease specified in the preamble "is not practicing the claimed method." *Id.* at 1334.

In the present case, as in *Jansen*, the Claim 1 preamble specifies the intentional purpose for which the method must be performed, *viz.*, to treat disorders of the nose and eye, and it is evident that the inventor limited his claim to treatment of those particular conditions.

Accordingly, under *Jansen*, the Court should construe this preamble language as a claim limitation.

Such a construction is supported by the Federal Circuit's decision in *Eaton Corporation v. Rockwell International Corporation*, 323 F.3d 1332, 1342 (Fed. Cir. 2003), also cited by Apotex. In *Eaton*, the Federal Circuit held that preamble language was limiting where the preamble did "much more than state an intended use of the invention" and where the method steps relied on preamble language for their operation. In *Eaton*, the court concluded that "the inventor chose to use both the preamble and the body of the claim to define his invention." *Id.* The '194 patentee similarly defined his invention through both the preamble and body of Claim 1.

*Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368 (Fed. Cir. 2001), on which Apotex relies, is inapposite. In that case, the court found preamble language non-limiting where the patentee sought one construction for purposes of validity and another construction for purposes of infringement. *Bristol-Myers Squibb*, 246 F.3d at 1376. The preamble language at issue described a "method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity." *Id.* at 1375-76. The patentee sought to limit the claims to methods that achieved the stated purpose for the validity analysis, but to broaden the claims to encompass all methods that carried out the physical steps for the infringement analysis. The court stressed the inconsistency in the patentee's position and concluded that the preamble did "not result in a manipulative difference in the steps of the claim." *Id.* at 1376.

Here, however, the preamble determines critical elements of the claimed method for both invalidity and infringement purposes. For example, the method ("applying [azelastine] directly

to nasal tissues or to the conjunctival sac of the eye") would be performed differently depending on whether the method is intended to treat "irritation or disorders of the nose and eye" or, for instance, irritation or disorders of the skin. In the former case, the method is carried out so that the drug stays locally in the nose or eye, whereas in the latter case the method would be carried out (*i.e.*, the formulation would be designed) so that the active drug substance travels from the nose into the bloodstream and to the skin. The method would also be performed differently with regard to, *inter alia*, dosage frequency and dosage amounts if azelastine were applied to the nose or eye to achieve systemic bloodlevels of the drug effective for treating other disorders. *See Bristol-Myers Squibb Co.*, 246 F.3d at 1375 (reasoning that language was not limiting because it did not alter dosage amounts recited in the claims or specification). The Claim 1 preamble is necessary to disclose appropriate limitations on the method of applying azelastine directly to nasal tissues or to the conjunctival sac of the eyes.

Apotex argues in the alternative that if the Claim 1 preamble is limiting, MedPointe's construction is inadequate in that it does not cover all of the diseases and symptoms taught in the patent. Apotex is simply wrong. As explained in detail in MedPointe's opening brief, each illness disclosed in the patent specification is encompassed by the terms rhinitis and/or conjunctivitis. (MedPointe Op. Br. at 6-8) Apotex argues that the term "irritation or disorders of the nose and eye" must include conditions from the specification "***and more***, including diseases and symptoms having infectious, allergic and non-specific etiologies." MedPointe's definition encompasses all diseases and symptoms contemplated by the specification, which are all types of rhinitis and/or conjunctivitis having infectious (*e.g.*, common cold, also known as viral rhinitis), allergic (*e.g.*, allergic rhinitis, allergic conjunctivitis) and non-specific (*e.g.*, vasomotor rhinitis) etiologies. The claim, as confirmed by the specification, simply does not cover non-rhinitis and

non-conjunctivitis diseases and symptoms.

For at least these reasons, MedPointe respectfully requests that the Court construe the phrase "irritation or disorders of the nose and eye" to mean "Rhinitis and/or conjunctivitis, including seasonal allergic rhinitis and vasomotor rhinitis. Symptoms of rhinitis include itching (also known as "pruritus"), sneezing, increased secretions (also known as "rhinorrea"), and congestion."

B. "Applying Directly To Nasal Tissues Or To The Conjunctival Sac Of The Eyes"

As set forth in MedPointe's opening brief, the phrase "applying directly to nasal tissues or to the conjunctival sac of the eyes" should be construed to mean "Topical application to the nose or to the conjunctival sac of the eyes. Excludes oral and parenteral applications." MedPointe's definition is supported by the plain and ordinary meaning, the specification and the prosecution history of the '194 patent.

MedPointe's exclusion of oral and parenteral applications is required by the intrinsic evidence. The proposed construction excludes oral administration because the specification disclaims that manner of treatment. *See Honeywell Int'l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1320 (Fed. Cir. 2006). According to the specification, the problems associated with oral administration were overcome by the disclosed topical applications. Ex. 2, col. 1, l. 56 - col. 2, l. 2. As the patent notes, "the invention provides a way to overcome problems which arise because of azelastine's exceptionally penetrating, bitter taste . . . . This problem has hitherto prevented oral application of azelastine solutions, since patients refuse to take such azelastine solutions or suspensions." *Id.* Both oral and parenteral administration of azelastine were disavowed in the '194 patent's prosecution history. The applicant distinguished the invention of the '194 patent from the prior art because the prior art disclosed only parenteral and oral applications of

azelastine, rather than the claimed direct application to nasal tissues or to the eye. *See* Ex.3, MP0095; *Philips*, 415 F.3d at 1317.

Apotex does not assert that oral and parenteral applications should be included within the claim scope. Rather, Apotex argues that "whether a particular accused infringing use or a particular prior art reference meets the limitations of 'applying directly' poses a question of fact" that would be inappropriate to resolve with claim construction. (Apotex Opening Br. at 7-8) Apotex's argument is a non-sequitur. MedPointe is not arguing for any particular claim application at this stage. MedPointe is only arguing that, as a matter of claim construction, oral and parenteral administration must be excluded based on the intrinsic evidence. Courts have repeatedly construed claims to exclude certain features on this basis. *See, e.g., AFG Industries, Inc. v. Cardinal IG Co., Inc.*, 239 F.3d 1239, 1250 (Fed. Cir. 2001) (holding that "[c]onsistent with the specification, we conclude that 'layer' should be interpreted as: 'a thickness of material of substantially uniform chemical composition, ***but excluding*** interlayers having a thickness not to substantially affect the optical properties of the coating'"); *Microsoft Corp. v. Multi-Tech Systems, Inc.*, 357 F.3d 1340, 1350 -1351 (Fed. Cir. 2004) (concluding that "the district court properly interpreted the 'sending,' 'transmitting,' and 'receiving' limitations of the 627, 649, and 532 patents as requiring the direct transmission of data packets between the local and remote sites over a telephone line ***and excluding*** the use of a packet-switched network such as the Internet").

For at least these reasons, MedPointe respectfully requests that the Court construe the phrase "applying directly to nasal tissues or to the conjunctival sac of the eyes" to mean "Topical application to the nose or to the conjunctival sac of the eyes. Excludes oral and parenteral applications."

C. "Azelastine And Its Physiologically Acceptable Salts"

As set forth in MedPointe's opening brief, the phrase "azelastine and its physiologically acceptable salts" should be construed to mean "Azelastine and salts of azelastine that are physiologically safe, effective, and tolerable, such as azelastine hydrochloride." MedPointe's proposed construction is supported by the plain and ordinary meaning and the specification.

Physiology is the "branch of medical science that deals with the ***healthy functions of different organs***." Ex. 4, Black's Medical Dictionary 540 (35th ed. 1987) (emphases added). Accordingly, the term "physiologically acceptable" requires the azelastine salt to be safe, effective and tolerable to the healthy functioning of different organs. This construction is supported by the specification, which discloses that "the object of the present invention is to provide a ***well tolerated and improved remedy*** based on azelastine or its salts for the treatment both of the allergy-related and vasomotor-related conditions as well as rhino virus-related cold and its accompanying symptoms." Ex. 2, col. 2, ll. 3-8.

Apotex advances several flawed arguments as to why the term "physiologically acceptable salts" should be construed to mean "a salt form of azelastine capable of being administered to an animal via at least one route of administration." First, Apotex argues that because there is no evidence that all of the azelastine salts listed in the specification were safe, effective, and tolerable when applied directly to nasal tissues or to the conjunctival sac of the eye, the term "physiologically acceptable" must mean something different. "Physiologically acceptable," however, must be read in the context of the entire specification, which teaches the safe, effective and tolerable use of azelastine in human patients. The specification states plainly that the goal of the invention is to "provide a ***well tolerated and improved remedy*** based on azelastine or its salts." Ex. 2, col. 2, ll. 4-5. It even discusses improved taste among human trial

subjects. *Id.* at col. 1, ll. 63-66. The entire patent focuses on safe, effective and tolerable preparations of azelastine for human beings.

Contrary to Apotex's assertion, the specification's lack of evidence regarding the safety and efficacy of all the listed salt forms is irrelevant. The specification lists only "***[p]ossible*** acid components for azelastine salts." *Id.* at col. 3, ll. 48-56. The patent specification does not say that all of the acid components listed are ***physiologically acceptable***. *See Johnson & Johnston Associates Inc. v. R.E. Service Co., Inc.*, 285 F.3d 1046, 1052 (Fed. Cir. 2002) ("[T]he claims, not the specification, provide the measure of the patentee's right to exclude. *Milcor Steel Co. v. George A. Fuller Co.*, 316 U.S. 143, 146, 62 S.Ct. 969, 86 L.Ed. 1332 (1942) ("Out of all the possible permutations of elements which can be made from the specifications, he reserves for himself only those contained in the claims.")). Only the salts disclosed in the specification that are physiologically acceptable are claimed.

Apotex's second argument is based on the patent specification's discussion of "physiologically acceptable" solvents. Apotex attempts to argue that because certain solvents might be "physiologically acceptable" for certain formulations but not for others, the term "physiologically acceptable" does not connote safety, efficacy and tolerability. This argument makes no sense. To the extent that Apotex's argument can be understood, Apotex appears to propose that "physiologically acceptable" means "***acceptable*** for any manner of administration to an animal." (Apotex Op. Br. at 10) This does not resolve the question of what "acceptable" means and entirely ignores the word "physiologically." In addition, as discussed earlier, the '194 patent focuses exclusively on remedies for human disease and does not contemplate administration to other animals. The term "physiologically acceptable" is properly interpreted as acceptably safe, effective and tolerable for human administration.

Lastly, Apotex contends that, as a matter of law, a method of treatment claim cannot require safety or efficacy. But the case law Apotex relies on to support its argument is inapposite. For example, Apotex relies on *Bristol-Myers Squibb*, which analyzed whether preamble language was limiting. 246 F.3d at 1375-76. The *Bristol-Myers Squibb* court did not address the issue whether a claim term such as "physiologically acceptable" can be construed in light of overwhelming intrinsic evidence to incorporate safety and efficacy requirements. The issue in the present case is not whether preamble language can be interpreted to impose safety and efficacy limitations on the claim, but whether a particular term in the body of the claim, read in light of the entire specification, is appropriately construed to incorporate these concepts.

Apotex's other cited case is also distinguishable. In *Purdue Pharma L.P. v. Endo Pharmaceuticals Inc.*, 438 F.3d 1123 (Fed. Cir. 2006), the Federal Circuit held that the terms at issue there, construed in light of the specification, could not impose a very specific efficacy limitation. The court held that the terms "controlled release" and "invention itself" could not "require acceptable pain control in approximately 90% of patients over a four-fold dosage range," because "the claims contain no limitations relating to the effectiveness of dosages in controlling pain in patients, and it is the claims ultimately that define the invention." *Id.* at 1136. In contrast, the plain meaning of the term "physiologically acceptable" at issue here incorporates concepts of safety, efficacy, and tolerability.

Apotex accuses MedPointe of proposing a claim construction that impermissibly imports FDA requirements into the term "physiologically acceptable." But MedPointe does no such thing. "Physiologically acceptable" incorporates general concepts of safety, tolerability, and efficacy. MedPointe seeks only to recognize these concepts in the Court's claim construction. While protesting against MedPointe's ordinary meaning construction, Apotex improperly seeks

to strip the term of all meaning. Under Apotex's proposed construction, "physiologically acceptable" would mean nothing more than that one could administer the compound to an animal. Apotex's proposed construction would include, for example, lethal injections. This fact confirms that Apotex's proposed construction renders the term "physiologically acceptable" meaningless. And Federal Circuit precedent is settled that claims should not be construed to eliminate claim limitations. *See Innova/Pure Water, Inc. v. Safari Water Filtration Systems, Inc.*, 381 F.3d 1111, 1119 (Fed. Cir. 2004) (while observing that a party's interpretation read the term "operatively" out of the phrase "operatively connected," the Court noted that "[w]hile not an absolute rule, all claim terms are presumed to have meaning in a claim.")

For at least these reasons, MedPointe respectfully requests that the Court construe the phrase "azelastine and its physiologically acceptable salts " to mean "Azelastine and salts of azelastine that are physiologically safe, effective, and tolerable, such as azelastine hydrochloride."

D. "A Medicament"

As set forth in MedPointe's opening brief, the term "a medicament" should be construed to mean "A product that includes a medicinal substance that has acceptable safety, efficacy, and tolerability for use in humans." MedPointe's proposed construction is the plain and ordinary meaning of that term and is supported by the testimony of Apotex's experts.

The dictionary definition of the term "medicament" is "a healing substance; medicine; remedy." Ex. 5, The Random House Dictionary of the English Language 1194 (2d ed. 1987). If a product is to be a "healing substance," "medicine" or "remedy," it must be able to be administered (tolerability) and improve health (efficacy) without causing a simultaneous detriment (safety). In other words, it must be safe, effective and tolerable.

Apotex's proposed construction ignores the plain and ordinary meaning of the term, as well as the teachings of the specification and the prosecution history. Apotex's strategy is clear. By pushing an overly broad construction of "medicament," Apotex hopes to bolster its invalidity positions. But Apotex's arguments are meritless.

Apotex's efforts to broaden the claim to include active ingredients "not named or even considered by the inventor" is unsupported by precedent.[1] According to Apotex, the use of the word "contains" in the phrase "a medicament which contains" means that the medicament can contain additional components and that the term is in "no way limited by the other claims, the patent specification, or the file history." Apotex's position is untenable.

In *Tap Pharmaceutical Products, Inc. v. Owl Pharmaceuticals, L.L.C.*, the Federal Circuit reviewed the district court's construction of the term "containing" in the following claim language: "A prolonged release microcapsule for injection, which comprises ***particles containing a water-soluble drug, the particles being dispersed in a spherical microcapsule matrix***. . . ." 419 F.3d 1346, 1353 -54 (Fed. Cir. 2005). The Federal Circuit affirmed the district court's construction that the term "containing" in this context required the particles to be composed of a drug and a drug-retaining substance. *Id.* The court rejected the argument that, in this context, "containing" was as broad as the term "comprising," *i.e.*, having at least the named component but possibly additional ingredients. The Federal Circuit noted that "it was entirely reasonable for the district court to look to the specification as well as extrinsic evidence to determine the manner in which the term was used in the [] patents at issue." *Id.*

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[1] Apotex argues that the dependent claims of the '194 patent show that the medicament of Claim 1 may contain preservatives, a solvent and any concentration of azelastine. This point, however, does not support its position that Claim 1 can include medicaments with additional active ingredients.

As in *Tap*, in the present case, the term "contains" is not a term of art and should be construed in light of the specification. There is no support in the specification (and Apotex provides none) for a construction of the term "contains" that would encompass additional active ingredients. "Contains" should not be interpreted as synonymous with the term of art "comprising" in this context. Indeed, the '194 patent specification makes clear that azelastine is the only active ingredient contemplated by the inventor. Ex. 2, col. 2, ll. 3-5 ("the object of the present invention is to provide a well tolerated and improved remedy based on azelastine or its salts").

The cases cited by Apotex do not contradict the proper construction of the term "containing" set forth in *Tap*. Apotex relies on *Genentech, Inc. v. Chiron Corporation*, 112 F.3d 495 (Fed. Cir. 1997) for the proposition that "containing," "comprising" and "including" are synonymous and mean that the claim does not exclude additional components or steps. This description of the case is misleading. The claim at issue in *Genentech* did not include the term "containing," and the *Genentech* court did not construe this term or state that it was synonymous with "comprising" or "including" as Apotex contends. Instead, the claim used the term "comprising," which the court explained "is a term of art used in claim language which means that the named elements are essential, but other elements may be added." 112 F.3d 495, 501 (Fed. Cir. 1997).[2]

Another case that Apotex cites, *Gillette Co. v. Energizer Holdings, Inc.*, also does not construe or discuss the term "containing," but instead construes "comprising." This case, nonetheless, supports the *Tap* approach of looking to the specification to determine the

[2] The other case cited by Apotex similarly construes the term of art "consisting of" and not the term "containing." *See Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1382 (Fed. Cir. 2000).

appropriate construction of a claim term. In *Gillette*, the Court held that a four-blade safety razor could infringe a claim "comprising. . . a group of first, second, and third blades" in part because "the specification's focus on blade exposures and express reference to 'blade units with a plurality of blades,'" showed that the invention covered razors with more than three blades. *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1371 (Fed. Cir. 2005) (internal citations omitted).

Unlike the patent specification at issue in *Gillette*, the specification in the '194 patent does not disclose medicaments with additional active ingredients and instead explicitly teaches that azelastine is the only active ingredient in the medicaments envisioned by the inventor. *See* Ex. 2, Abstract ("A medicament . . . which contains ***as active ingredient azelastine or a physiologically acceptable salt.***") (emphases added); col. 2, ll. 3-5 ("the object of the present invention is to provide a well tolerated and improved remedy ***based on azelastine or its salts***. . . ") (emphases added); col. 6, ll. 7-9 ("Example 1: Nasal spray or nasal drops or eye drops with 0.1% ***azelastine hydrochloride as active ingredient.***") (emphases added). Apotex wants to broaden the claim to include multiple active ingredients to bolster its invalidity arguments, but such a construction is flatly contradicted by the intrinsic evidence.

Apotex further argues that there is no indication that the term "a medicament" should be construed to require safety, efficacy and tolerability in humans when applied directly to the eyes or nose.[3] The patent read as a whole, however, would indicate to a person of ordinary skill in the art that the "medicament for nasal use or for use in the eye which contains as active ingredient

[3] Contrary to Apotex's apparent over-reading of MedPointe's proposed construction, MedPointe contends that "a medicament" means a medicinal substance that has acceptable safety, efficacy and tolerability for use in humans, not that it necessarily has acceptable safety, efficacy and tolerability ***when applied directly to the nose or eyes.*** Other aspects of the claim capture that concept.

azelastine or a physiologically acceptable salt" was intended for humans.[4] Ex. 2, Abstract. For example, the specification states that "the object of the [] invention [was] to provide a well tolerated and improved remedy based on azelastine." *Id.* at col. 2, l. 3-5. The specification's focus on how the invention overcame the unusually bitter taste of azelastine strongly supports the view that the invention is intended to be a treatment for human disorders. The specification states explicitly that azelastine's exceptionally bitter taste caused "patients [to] refuse to take such azelastine solutions or suspensions" and that "[i]t was surprisingly found in trial subjects that this bitter taste was no longer in evidence when the azelastine formulations of the invention were sprayed into the nose." *Id.* at col. 1, l. 60 - col. 2, l. 2.

For at least these reasons, MedPointe respectfully requests that the Court construe the phrase "a medicament" to mean "A product that includes a medicinal substance that has acceptable safety, efficacy, and tolerability for use in humans."

E. "The Medicament Contains 0.003 to 0.5% (Weight/Weight) Of Azelastine Or An Amount Of A Physiologically Acceptable Salt Of Azelastine Which Contains 0.003 To 0.5% (Weight/Weight) Azelastine"

As set forth in MedPointe's opening brief, the phrase "the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine" should be construed to mean "The medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine in which the weight of azelastine base is 0.003 to

[4] Apotex's repeated attacks on the presumptive validity of the '194 patent throughout its claim construction brief (*see, e.g.*, Apotex Op. Br. at 15) are irrelevant to the Court's claim construction analysis. At trial, Apotex will not be able to meet its burden of proving invalidity by clear and convincing evidence. The trial will show that Chand *et al.*, 58 ANN. ALLERGY 344-49 (1987), and the other prior art cited by Apotex in its opening brief are not sufficient for Apotex to meet its burden of proving invalidity by clear and convincing evidence.

0.5% of the weight of the medicament. Includes a 0.0033 to 0.55% (weight/volume) aqueous solution of azelastine hydrochloride."

The parties agree that the phrase applies to azelastine and salts of azelastine wherein "the weight of azelastine base is 0.003 to 0.5% of the weight of the medicament." MedPointe proposes that the definition also include the weight/volume percentage of azelastine hydrochloride in light of the specification's disclosure that in the case of solutions and suspensions, the azelastine dosage should be measured in terms of weight per volume of solution. Ex. 2, col. 4, ll. 10-13 ("In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/weight of the formulation."). This is not controversial as Apotex has already agreed to stipulate to infringement of the only claim in which this term appears, Claim 4.

F. "Aqueous Solution"

As set forth in MedPointe's opening brief, the phrase "aqueous solution" should be given its plain and ordinary meaning as understood by a person of ordinary skill in the art. The dictionary definition of "aqueous solution" is "[a] solution with the solvent as water." Ex. 6, McGraw-Hill Dictionary of Chemical Terms 31 (1985). The same dictionary defines "solution" as "[a] single, homogeneous liquid, solid, or gas phase that is a mixture in which the components (liquid, gas, solid, or combinations thereof) are uniformly distributed throughout the mixture." *Id.* at 400. Given these straightforward definitions, MedPointe contends that no claim construction would further clarify these terms. As a result, no claim construction is necessary.

Apotex offers a strained construction of "aqueous solution" that is unsupported by the plain and ordinary meaning or the specification. Indeed, Apotex makes no effort to hide its attempt to read the kitchen sink into this term to bolster its invalidity arguments. Apotex argues

that the term "aqueous solution" should be construed to mean "a formulation wherein the excipients, preservatives, and/or active ingredients are dissolved in a solvent and the solvent is water." The plain and ordinary meaning of "aqueous solution" simply does not include the addition of excipients, preservatives, or active ingredients. Further, neither the specification nor the claims contemplate the addition of any other active ingredient, as explained above.

In support of its proposed construction, Apotex advances the untenable argument that "aqueous solution" includes azelastine in a ***mixture*** of water with additional solvents, *e.g.*, alcohols and polyglycols. The specification, however, differentiates between aqueous ***solutions*** and aqueous ***mixtures***. A solution, in which multiple components are uniformly distributed throughout a single phase, is a type of mixture. Ex. 6, McGraw-Hill Dictionary of Chemical Terms 400 (1985). But a mixture may not be a solution, and more generally means "substances that are mixed, but not chemically combined." Ex. 7, Grant & Hackh's Chemical Dictionary 373 (1987). Simply put, all solutions are mixtures, but not all mixtures are solutions.

The specification recognizes this difference, stating "[t]he solvent used is preferably water or ***mixtures*** of water with other physiologically acceptable solvents (for example those mentioned above). Preferably, the amount of the latter solvent in the ***aqueous mixture*** should not exceed 15% by weight." Ex. 2, col. 2, ll. 41-45. The specification contemplates that the "liquid polyglycols (molecular weight 200 to 600)" may not form a solution with water. Instead, the mixture may form an emulsion, *id.* at col. 3, l. 28, which is "a stable dispersion of one liquid in a second immiscible liquid." Ex. 6, McGraw-Hill Dictionary of Chemical Terms 152 (1985). Therefore, the term "aqueous solution" as used in the specification and Claim 7 should not be defined to include "aqueous mixtures."

For at least these reasons, MedPointe respectfully contends that the phrase "aqueous

solution" requires no construction.

G. "Solution"

As set forth in MedPointe's opening brief, the term "solution" should also be given its plain and ordinary meaning. As stated above, the dictionary definition of "solution" is "[a] single, homogeneous liquid, solid, or gas phase that is a mixture in which the components (liquid, gas, solid, or combinations thereof) are uniformly distributed throughout the mixture." Ex. 6, McGraw-Hill Dictionary of Chemical Terms 400 (1985). No claim construction is required to further clarify or define this term.

Apotex argues that "solution which contains" should be construed to mean "the medicament of claim 1 wherein any excipients, a preservative and active ingredients are dissolved in a solvent and the preservative is either thimerosal or benzalkonium in the stated concentrations." Apotex also argues that the preferred solvents include "alcohols, polyglycols, and/or water." These arguments have no support.

The plain and ordinary meaning of "solution" does not include the addition of excipients, preservatives, or active ingredients. Reference to any dictionary confirms this fact. Further, neither the specification nor the claims contemplate the addition of any other active ingredient, as explained above.

Apotex argues that the preferred solvents include "alcohols, polyglycols, and/or water." But while the specification lists these solvents, it further states "[t]he solvent used is ***preferably water or mixtures of water*** with other physiologically acceptable solvents (for example those mentioned above). Preferably, the amount of the latter solvent in the aqueous mixture should not exceed 15% by weight." Ex. 2, col. 2, ll. 41-45 (emphases added). In other words, the patent teaches using solvents with ***mostly water***. The Court should reject Apotex's improper attempt to

redefine the simple and well understood term "solution."

For at least these reasons, MedPointe respectfully contends that the term "solution" requires no construction.

H. "Applied By Spraying"

The parties have previously disputed whether "applied by spraying" in Claim 9 is limited to an "aqueous solution," advanced by MedPointe, or "solutions (including aqueous solutions), suspensions and powders," advanced by Apotex. Although the intrinsic and extrinsic evidence supports MedPointe's original proposed construction, *viz.*, limiting "applied by spraying" to an "aqueous solution," MedPointe is not opposed to a claim construction that allows "applied by spraying" to include "solutions or suspensions." Adopting this construction will not substantively affect the issues in this case and eliminates a needless claim construction dispute. MedPointe, therefore, proposes a construction modified slightly from its opening brief in an effort to narrow and focus the issues for the Court and reduce the disputes between the parties.

MedPointe's new proposal seeks to have the Court construe the phrase "applied by spraying" to mean "Delivering a fixed volume (typically, 50 to 150 microliters) of a solution or suspension to nasal tissues by aerosolizing that solution or suspension into a fine mist (typically with the size of most droplets falling in the range of 10 to 250 micrometers) targeted to those tissues. Excludes application to the eye and excludes application of drops to the nose."

Apotex argues that MedPointe is importing limitations that do not appear in either the claim language or the specification. MedPointe's proposed construction, however, is required by the specification, which discloses spraying azelastine in a solution or suspension in a certain volume and with a certain droplet size to nasal tissues. For example, the specification confirms that a range of 50 to 150 microliters is typical in stating that "the dosage per nostril is, for

example, 0.01 to 0.2 ml, in particular ***0.05 to 0.15 ml***." Ex. 2, col. 3, ll. 40-41. The examples in the specification, which disclose providing a fixed medicament volume of 50 microliters and 140 microliters, also confirm MedPointe's proposed construction that requires delivery of a fixed volume of "typically, 50 to 150 microliters." *Id.* at col. 7, l. 15 (describing 50 microliters per actuation); col. 6, l. 28 (describing 140 microliters per actuation).

The specification further supports MedPointe's proposed construction that requires "aerosolizing that solution or suspension into a fine mist" of droplets sized between 10 and 250 micrometers (microns). A person of ordinary skill in the art would understand that a nasal spray, designed to treat disorders of the nose, should contain droplets that fall within the range of 10 to 250 micrometers, because droplets that are smaller than 10 micrometers will not be retained in the nose but will travel from the nose into the lungs, thereby negating the therapeutic value of the nasal spray and introducing the nasal spray into unintended targets. *See* Ex. 8, Remington's Pharmaceutical Sciences 1491 (14th ed. 1970) ("The spray device should produce relatively coarse droplets if the action of the drug is to be restricted to the upper respiratory tract. Fine droplets tend to penetrate farther into the respiratory tract than is desirable."). Indeed, the specification indicates that the claimed invention is intended to treat conditions of the nose and eye, but not the lung. *See* Ex. 2, col. 1, ll. 6-7 ("The present invention relates to the treatment of nasal and eye tissues with azelastine.").

Apotex argues that spraying a solution produces drops of the solution and that MedPointe is importing a limitation by excluding drops. Apotex's argument misrepresents the language of the specification. According to Apotex, "spraying of a solution results in drops of a solution is also described. (Ex. A, the '194 patent, col. 5:36-38)" (Apotex Op. Br. at 19) The specification, however, teaches that ***droplets***, not drops, are formed by a spray: "The subsequent very sudden

vaporization of the propellant tears the solution or suspension of azelastine into the finest ***droplets or minute particles*** which can be sprayed into the nose or which are available for inspiration into the nose." Ex. 2, col. 5, ll. 36-41.

MedPointe's proposed construction does not import limitations. "Applying by spraying" cannot include application by drops or, for that matter, powders. The specification and prosecution history repeatedly distinguish between sprays, drops and powders. The patent specification discloses different forms of the invention such as "***drops***, ointments, creams, gels, insufflatable ***powders*** or, in a particularly preferred embodiment, in the form of a ***spray*** (preferably a nasal spray)." Ex. 2, col. 2, ll. 14-17. According to the applicant during the prosecution history of the '194 Patent: "***Claims 9-11 relate to more preferred modes of application*** of the azelastine-containing composition." Ex. 3, MP0113 (emphases added) Claims 9, 10 and 11 specifically claim modes of application by spraying, drops, and powders, respectively. The term "applied by spraying" therefore cannot include applying by drops or powders, as Apotex's proposed construction allows, under the doctrine of claim differentiation. *See Innova/Pure Water, Inc. v. Safari Water Filtration Systems, Inc.*, 381 F.3d 1111, 1123 (Fed. Cir. 2004) ("'different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope'").

Apotex also contends that spraying includes application to the eyes and that MedPointe's construction imports a limitation. Apotex points to the portion of the specification that states, "[t]he preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used in the form of drops, ointments, creams, gels, insufflatable powders or, in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray)." Ex. 2, col. 2, ll. 12-17. This language, however, does not provide

that "spray" in the '194 patent somehow includes the world's first eye spray. Indeed, Apotex's own medical expert, Dr. Schwartz, testified that

Q.

**REDACTED**

the specification discloses that either "conventional spray" hardware can be used for the nasal spray or, preferably, "nasal spray" hardware can be used. This distinction is clear in the nasal spray discussion of Example 1: "This is filled into plastic bottles which are closed with a ***conventional spray insert or*** into plastic or

glass bottles which are closed with a conventional pump sprayer. In the latter case, pumps with ***nasal spray inserts*** are, for example used . . . ." *Id.* at col. 6, ll. 23-27. In this example, as well as the rest of the specification, there is no suggestion that an eye spray was ever contemplated by the inventor.

For at least these reasons, MedPointe respectfully requests that the Court construe the phrase "applied by spraying" to mean "Delivering a fixed volume (typically, 50 to 150 microliters) of a solution or suspension to nasal tissues by aerosolizing that solution or suspension into a fine mist (typically with the size of most droplets falling in the range of 10 to 250 micrometers) targeted to those tissues. Excludes application to the eye and excludes application of drops to the nose."

III. UNASSERTED CLAIM 12

As MedPointe stated in its opening brief, in an effort to narrow and focus the issues, MedPointe is no longer asserting Claim 12 of the '194 patent in this action. MedPointe informed Apotex of this fact on December 17, 2007. Apotex has agreed to stipulate to infringement of Claims 4, 5, 7, 8, and 9 and there is no need or basis for the parties to dispute Claim 12 further in this action. Because Claim 12 is an independent claim, on which no other claims at issue depend, there is no controversy regarding Claim 12. Therefore, it is entirely unnecessary and would be inappropriate for the Court to construe the terms of Claim 12.

## CONCLUSION

For the foregoing reasons and those set forth in MedPointe's opening claim construction brief (D.I. 105), MedPointe respectfully requests that the Court adopt its proposed constructions of the disputed claim terms and phrases.

Kelly E. Farnan
Frederick L. Cottrell, III (#2555)
cottrell@rlf.com
Kelly E. Farnan (#4395)
farnan@rlf.com
RICHARDS, LAYTON & FINGER P.A.
One Rodney Square
P.O. Box 551
Wilmington, Delaware 19899
(302) 651-7700

*Attorneys for Plaintiff*
*MedPointe Healthcare Inc.*

*Of Counsel:*

John M. Desmarais
Peter J. Armenio
Anne S. Toker
KIRKLAND & ELLIS LLP
Citigroup Center
153 East 53rd Street
New York, New York 10022
(212) 446-4800

Dated: January 9, 2008

**CERTIFICATE OF SERVICE**

I hereby certify that on January 9, 2008, I electronically filed the foregoing with the Clerk of Court using CM/ECF, which will send notification of such filing, and hand delivered to the following:

Richard L. Horwitz
Potter Anderson & Corroon LLP
Hercules Plaza, 6th Floor
1313 N. Market Street
Wilmington, DE 19801

I hereby certify that on January 9, 2008, I sent the foregoing document by electronic mail to the following non-registered participant:

A. Sidney Katz
Robert B. Breisblatt
Steven E. Feldman
Stephen P. Benson
WELSH & KATZ, LTD.
120 South Riverside Plaza, 22nd Floor
Chicago, IL 60606
askatz@Welshkatz.com
rbbreisblatt@welshkatz.com
sefeldman@welshkatz.com
sbenson@welshkatz.com

Kelly E. Farnan (#4395)
farnan@rlf.com

**UNITED STATES DISTRICT COURT**
**DISTRICT OF DELAWARE**

**CERTIFICATE OF SERVICE**

I HEREBY CERTIFY that on January 15, 2008, I electronically filed the foregoing document with the Clerk of Court using CM/ECF and caused the same to be served on the plaintiff at the address and in the manner indicated below:

**BY HAND DELIVERY**

Richard L. Horwitz
Potter Anderson & Corroon LLP
Hercules Plaza, 6th Floor
1313 N. Market Street
Wilmington, DE 19801

I hereby certify that on January 15, 2008, the foregoing document was sent to the following non-registered participants in the manner indicated:

**BY FEDERAL EXPRESS**

A. Sidney Katz
Robert B. Breisblatt
Steven E. Feldman
Stephen P. Benson
Welsh & Katz, Ltd.
120 South Riverside Plaza, 22nd Floor
Chicago, IL 60606

Kelly E. Farnan

Kelly E. Farnan (#4395)

# EXHIBIT 1

**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

| | |
|---|---|
| MEDPOINTE HEALTHCARE INC.,<br><br>Plaintiff,<br><br>v.<br><br>APOTEX INC. and APOTEX CORP.,<br><br>Defendants. | C.A. No. 06-164-SLR |

**CLAIM CONSTRUCTION ORDER**

After considering the submissions of the parties and hearing oral argument on the matter, IT IS HEREBY ORDERED this _____ day of _____, 2008 that the Court construes the disputed claim limitations of the patent in suit as follows:

**U.S. Pat. No. 5,164,194**

1. Claims 4, 5, 7, 8 and 9: "irritation or disorders of the nose and eye" means "Rhinitis and/or conjunctivitis, including seasonal allergic rhinitis and vasomotor rhinitis. Symptoms of rhinitis include itching (also known as "pruritus"), sneezing, increased secretions (also known as "rhinorrea"), and congestion."

2. Claims 4, 5, 7, 8 and 9: "applying directly to nasal tissues or to the conjunctival sac of the eyes" means "Topical application to the nose or to the conjunctival sac of the eyes. Excludes oral and parenteral applications."

3. Claims 4, 5, 7, 8 and 9: "azelastine and its physiologically acceptable salts" means "Azelastine and salts of azelastine that are physiologically safe, effective, and tolerable, such as azelastine hydrochloride."

4. Claims 4, 5, 7, 8 and 9: "a medicament" means "A product that includes a medicinal substance that has acceptable safety, efficacy, and tolerability for use in humans."

5. Claim 4: "the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine" means "The medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of

azelastine in which the weight of azelastine base is 0.003 to 0.5% of the weight of the medicament. Includes a 0.0033 to 0.55% (weight/volume) aqueous solution of azelastine hydrochloride."

6. Claim 7: "aqueous solution" should be given its ordinary meaning using the definitions of "aqueous" and "solution. "

7. Claim 8: "solution" should be given its ordinary meaning.

8. Claim 9: "applied by spraying" means "Delivering a fixed volume (typically, 50 to 150 microliters) of a solution or suspension to nasal tissues by aerosolizing that solution or suspension into a fine mist (typically with the size of most droplets falling in the range of 10 to 250 micrometers) targeted to those tissues. Excludes application to the eye and excludes application of drops to the nose."

Sue L. Robinson
United States District Judge

# EXHIBIT 2

US005164194A

# United States Patent [19]

Hettche

[11] Patent Number: 5,164,194

[45] Date of Patent: Nov. 17, 1992

[54] AZELASTINE CONTAINING MEDICAMENTS

[75] Inventor: Helmut Hettche, Dietzenbach, Fed. Rep. of Germany

[73] Assignee: Asta Pharma AG, Fed. Rep. of Germany

[21] Appl No.: 551,644

[22] Filed: Jul. 12, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 268,772, Nov 9, 1988, abandoned

[30] Foreign Application Priority Data

Nov 13, 1987 [DE] Fed Rep of Germany ..... 3738681

[51] Int. Cl.[5] ..... A61K 9/14; A61K 31/55

[52] U.S. Cl. ..... 424/489; 424/43; 424/45; 424/464; 424/422; 514/212

[58] Field of Search ..... 424/43, 464, 422, 45, 424/489; 514/212; 222/394; 141/24; 239/302; 248/108

[56] References Cited

U.S. PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 158,564 | 1/1875 | Barnes | 141/24 |
| 2,119,643 | 6/1938 | Mendl | 222/394 |
| 2,136,940 | 11/1938 | Ehbrecht | 222/394 |
| 2,457,024 | 12/1948 | Arp | 248/108 |
| 2,995,308 | 8/1961 | Ashkenez | 239/302 |
| 3,813,384 | 5/1974 | Vogelsang | 546/133 |
| 4,704,387 | 11/1987 | Engel et al. | 514/212 |
| 4,769,369 | 9/1988 | Thomas et al. | 514/234.5 |

FOREIGN PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 2164058 | 7/1972 | Fed. Rep. of Germany | 546/133 |
| 3530793 | 3/1986 | Fed. Rep. of Germany | 514/212 |
| 1377231 | 1/1972 | United Kingdom . | |

OTHER PUBLICATIONS

Negwer, Organic-Chemicals, Drugs and Their Synonyms, vol. II, (1987) p. 1145.

European Search Report.

Org.-Chem. drugs and their synonyms, vol. III, No. 6496 (1987).

Arzneimittel, Fortschritte 1972–1985, pp. 936 and 939 (1977).

*Primary Examiner*—Thurman K. Page

*Assistant Examiner*—Neil S. Levy

*Attorney, Agent, or Firm*—Cushman, Darby & Cushman

[57] ABSTRACT

A medicament for nasal use or for use in the eye which contains as active ingredient azelastine or a physiologically acceptable salt.

12 Claims, No Drawings

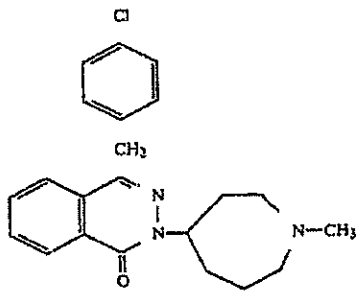
# AZELASTINE CONTAINING MEDICAMENTS

This is a continuation of application Ser. No 07/268,72, filed Nov. 9, 1988, now abandoned.

The present invention relates to the treatment of nasal and eye tissues with azelastine.

## BACKGROUND OF THE INVENTION

Azelastine is a phthalazinone derivative having the following structural formula:




The chemical designation is: 4-(4-chlorobenzyl)-2-(perhydro-1-methyl-azepine-4-yl)-1-(2H)phthalazinone. Azelastine is used in particular for prophylactic treatment of asthma. Azelastine also has anti-allergic and antihistamine properties, see German Patent No. 21 64 058

## SUMMARY OF THE INVENTION

It has now been found that azelastine and its physiologically acceptable salts display particularly advantageous and surprising effects when the corresponding formulations are applied directly in the nose and/or to the conjunctival sac of the eye.

Elimination or marked relief has thus been achieved not only in allergy-related rhinitis, but also in the normal common cold (caused, for example, by rhino viruses) as well as in the vasomotor cold and the symptoms of illness triggered thereby.

It is surprising in this context that local nasal application also has a favorable effect on the mucous membrane of the eye (elimination or relief of reddening of the eye and of eye irritation) so that the additional use of eye drops is frequently superfluous.

Other indications for the application/use of the invention are, for example: non-specific conjunctivitis, allergy-related conjunctivitis, allergic blepharoedema, catarrhal conditions in the eye or nose, coryza.

Surprisingly, in addition, none of the tiredness that arises with other applications was observed with use according to the invention.

Furthermore the invention provides a way to overcome problems which arise because of azelastine's exceptionally penetrating, bitter taste. The degree of the bitter taste is so intense that it is even found to be unpleasant in a dilution of 1 : 706. This problem has hitherto prevented oral application of azelastine solutions, since patients refuse to take such azelastine solutions or suspensions. It wa surprisingly found in trial subjects that this bitter taste was no longer in evidence when the azelastine formulations of the invention were sprayed into the nose. As a result, it is possible in this manner to apply solutions or suspensions of azelastine and its salts nasally without taste impairment. Moreover the bitter taste is barely perceptible when the sprayed azelastine solution or suspension runs down into the pharynx.



Therefore, the object of the present invention is to provide a well tolerated and improved remedy based on azelastine or its salts for the treatment both of the allergy-related and vasomotor-related conditions as well as rhino virus-related cold and its accompanying symptoms.

A further object of the present invention is to provide medical formulations which are adapted to direct application to nasal and eye tissues.

The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used in the form of drops, ointments, creams, gels, insufflatable powders or, in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. For example 0.03 to 3 mg of azelastine base should be released per individual actuation.

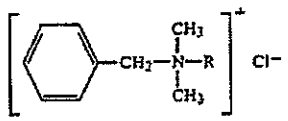
Through the use of nasal drops or a nasal spray, the dosage of azelastine required for the treatment of the cold is lowered approximately tenfold and hence the incidence of the appearance of side effects is considerably lower than in the case of the application of azelastine in orally taken dosage forms such as tablets or syrups which distribute the active substance throughout the entire body. In the treatment of a banal illness such as a cold, a low incidence of side effects is particularly important and thus represents a considerable medical advance.

Solvents which may preferably be used for the formulations of the invention are: water, saturated aliphatic mono and polyvalent alcohols which contain 2-3 carbon atoms (for example ethanol, isopropanol, 1,2-propylene glycol, glycerine), liquid polyglycols (molecular weight 200 to 600).

The solvent used is preferably water or mixtures of water with other physiologically acceptable solvents (for example those mentioned above). Preferably, the amount of the latter solvent in the aqueous mixture should not exceed 15% by weight.

The solutions or formulations preferably contain preservatives and stabilizers. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and their alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Furthermore, it is possible, for example, to use sodium-(2- ethylmercurithio)-benzoate generally known as "thimerosal" which may be present in an amount of 0.001 to 0.05, preferably from 0.005 to 0.02, for example 0.01% (weight/volume in liquid formulations, otherwise weight/weight). Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl- butyl)]phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl-γ-picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preserva-

tives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride". These latter consist of a mixture of the compounds of formula,



in which R represents an alkyl group having the formula $C_nH_{2n+1}$, wherein n represents a whole number from 8 to 18. The use of a mixture of compounds in which n represents 10 to 14 is particularly preferred and in particular the special compound in which $R=C_{12}H_{25}$ "Benzalkonium chloride" and the compounds of the above formula can be used in concentrations of 0.005 to 0.10, preferably of 0.005 to 0.05, for example of 0.01% (weight/volume for liquid formulations, otherwise weight/weight) and they may optionally be used in combination with 0.2 to 2.0, for example 0.4% (weight/ volume) of 2-phenylethanol

The formulations of the invention (solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, dosage aerosols) contain 0.0005 to 2, preferably 0.001 to 1, in particular 0.003 to 0.5% (weight/weight) of azelastine (related to the free azelastine base). Should the azelastine be present-as a salt, the amounts should be recalculated as necessary to give the amounts of azelastine itself mentioned above. In the case of the eye drops, the same azelastine concentrations apply as in the case of the nasal forms.

In the case of powders, the concentration of azelastine base is 0.0005 to 2 percent by weight related to the solid carrier substances.

In the case of solutions, the dosage per nostril is, for example, 0.01 to 0.2 ml, in particular 0.05 to 0.15 ml. Such a dosage should be applied once to several times, preferably 1 to 5 times daily (optionally also hourly).

In the case of use at the eye (eye drops) the dosage is for example 1 drop (about 0.05 ml) of the solution or corresponding amounts of the semi-solid formulation forms.

Possible acid components for azelastine salts are, for example: hydrohalic acids (HCl, HBr), sulphuric acid, phosphoric acids ($H_3PO_4$, metaphosphoric acid, polyphosphoric acids), nitric acid, organic mono-, di- or tricarboxylic acids of aliphatic, alicyclic, aromatic or heterocyclic organic acids (embonic acid, citric acid, tartaric acid), aliphatic and aromatic sulfonic acids (for example camphorsulfonic acid).

The total amounts of preservatives in the formulations (solutions, ointments, etc.) is between 0.001 to 0.10, preferably 0.01 g per 100 ml of solution/suspension or 100 g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used:

thimero sal 0.002–0.02%;

benzalkonium chlorie 0.002 to 0.02% (in combination with thimero sal the amount of thimero sal is, for example =0.002 to 0.005%;);

chlorhexidine acetate or gluconate 0.01 to 0.02%;

phenyl mercuric/nitrate, borate, acetate 0.002–0.004%;

p-hydroxybenzoic acid ester (for example a mixture of the methyl ester and propyl ester 7 : 3): 0.05–0.15, preferably 0.1%.

The preservative used is preferably a combination of edetic acid (for example as the disodium salt) and benzalkonium chloride. In this combination, the edetic acid is used in a concentration of 0.05 to 0.1%, benzalkonium chloride being used in a concentration of 0.005 to 0.05%, preferably 0.01%.

In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/-weight of the formulation.

Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides, polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerization of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine components.

In the case of dosage forms containing water, it is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.

The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50° to 0.56° C. is attained in comparison to pure water. In Example 1, for instance, such substances would be used in such an amount which is iso-osmotic with 68 g of sodium chloride (0.68%).

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example:

Glucose $1H_2O$ 3.81 g ; saccharose 6.35 g ; glycerine 2.2 g; 1,2-propylene glycol 1.617 g ; sorbitol 3.84 g (in the case of mixtures of these substances correspondingly less may optionally be used)

Moreover, it is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.s. Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In the event of the use of hydroxypropyl cellulose, 0.1% by weight are, for example, used for this purpose.

It is also possible to add to the formulations buffer substances such as citric acid / sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), tromethamol or equivalent conventional buffers in order, for example, to adjust the formulation to a pH value of 6 to 7.5, preferably 6.5 to 7.1.

The amount of citric acid is, for example, 0.01 to 0.14, preferably 0.04 to 0.05 g, the amount of disodium hydrogenphosphate 0.1 to 0.5, preferably 0.2 to 0.3 g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

In the case of solutions and suspensions, the maximum total concentration of active agent and buffer should be less than 5%, in particular less than 2% (weight-/volume)

For the nasal application a solution or suspension is preferably used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in the form of a solution or suspension in a so-called propellant. Propellants are pressurized liquid chlorinated, fluorinated hydrocarbons or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutane or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. The pressure packing has a dosage valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed into the nose or which are available for inspiration into the nose. Certain plastic applicators are used to actuate the valve and to convey the sprayed suspension into the nose. Propellants that may, however, also be used are: $CO_2$, nitrous oxide and compressed air.

In the case of application as an aerosol, it is also possible to use a conventional adapter.

When suspensions are used, the maximum particle size of the solid substances (azelastine +auxiliary substances) should not exceed 30 μm.

In the case of use in the form of an insufflatable powder, the maximum particle size of the substances should not be greater than 20 μm.

What occurs is, for example, a vaporizing of solid azelastine or its salts. In this case the azelastine or its salt is, for example, mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate. The concentration of azelastine is 1 part by weight of azelastine to 50 to 200,000 parts by weight of carrier substance (0.0005 to 2% of azelastine).

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention is illustrated by the following examples.

### EXAMPLE 1

Nasal spray or nasal drops or eye drops with 0.1% azelastine hydrochloride as active ingredient

The following are dissolved, in the following order, into 9.00 kg of water: 10 g of azelastine hydrochloride, 5 g of edetic acid disodium salt 2 $H_2O$, 68 g of sodium chloride, 1.25 g of alkyl-benzyldimethylammonium chloride (benzalkonium chloride), 4.38 g of citric acid, 64.8 g of sodium monohydrogen-phosphate. 12 $H_2O$ as well as 10 g of hydroxypropylmethyl cellulose.)[1]

[1] Commercially available product, for example methocel E4M premium

The solution obtained is diluted to 10.05 kg = 10 liters with water. The solution is filtered through a membrane filter of pore size 0.2 μm after careful mixing, the first 500 ml of filtrate being discarded. The filtrate has a pH value of 6.8 ±0.3. This is filled into plastic bottles which are closed with a conventional spray insert or into plastic or glass bottles which are closed with a conventional pump sprayer. In the latter case, pumps with nasal spray inserts are, for example used, which spray about 0.14 ml of solution per actuation. In this manner, 0.14 mg of azelastine hydrochloride are sprayed into the nose per actuation in the form of the solution.

If the above obtained filtrate is filled into the bottles with dropper pipettes conventionally used for nasal drops or eye drops, the solution can be dripped into the nose or eye using a dropper pipette.

### EXAMPLE 2

Nasal ointment with 0.1% of azelastine hydrochloride

5 kg of polyoxyethylene stearate[2], 8 kg of cetylstearyl alcohol (Lanette 0), 20 kg of white Vaseline, 15 kg of liquid paraffin and 0.5 kg of silicon oil are melted together in a heatable vessel. 126 g of p-hydroxybenzoic acid methyl ester and 53 g of p-hydroxybenzoic acid propyl ester are dissolved in the melt (temperature of the melt 80° C.). Subsequently, a solution heated to 70° C. of 0.1 kg of azelastine hydrochloride, 140 g of p-hydroxybenzoic acid methyl ester and 60 g of p-hydroxybenzoic acid propyl ester in 51.021 kg of purified water are emulsified with the aid of a high speed stirrer and the emulsion obtained is stirred until cold and repeatedly homogenized at regular time intervals.

[2] Polyoxyethylene-40-stearate, solid, white to cream-colored mass, D 25 ca 1.1, F 40°–44° C. Solidification point ca 41° C.

The ointment is filled into tubes which have a tubular extension beyond the thread and are thus particularly suitable for applying the ointment into the nose.

### EXAMPLE 3

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride per stroke

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about −55° C. in an appropriate cooling vessel. A mixture of 0.086 kg of precooled sorbitantrioleate and 0.8600 kg of precooled trichlorofluoromethane are dissolved with stirring into this mixture at −55° C. 0.0688 kg of micronized azelastine hydrochloride and 0.0688 kg of micron-

ized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about −55° C.

Following closure of the cooling vessel the suspension is again cooled to about −55° C. under intensive stirring. It is then ready to be filled.

With continued stirring the suspension is filled into the conventional suitable aluminum monobloc tins. The monobloc tins are closed immediately after the suspension has been filled using conventional dosage valves which release 0.05 ml of suspension per valve actuation. Actuation of the valve thus releases 0.5 mg of azelastine hydrochloride. Presentation is effected in conjunction with a conventional applicator which permits introduction of the active substance into the nose of the patient.

EXAMPLE 4

Eye drops with 0.05% of azelastine hydrochloride

140 g of polyvinylalcohol (trade name for example: Mowiol 26–88 / Hoechst AG, Frankfurt 80) are stirred into 4 liters of cold water for injection purposes, the suspension is heated to 90° C. and left at this temperature for 45 minutes. After cooling, the solution obtained is mixed with the following solutions:

5 g of azelastine hydrochloride in 1 liter of water for injection purposes, 0.2 g of phenyl mercuric nitrate in 2 liters of water for injection purposes, 70 g of sodium chloride in 1 liter of water for injection purposes.

The mixture is adjusted to a pH value of 6.8 through addition of 0.1 N sodium hydroxide solution, mixed with a solution of 15 g of sodium dihydrogen phosphate.2 $H_2O$ and 21 g of disodium hydrogen phosphate.2 $H_2O$ in 1 liter of water for injection purposes and filled up to 10 liters with water for injection purposes.

Following careful mixing the solution is filtered through a membrane filter of pore size 0.2 μm with glass fiber pre-filter and filled into sterile eye drop bottles under aseptic conditions after discarding a first 500 ml of filtrate.

What is claimed is:

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

2. A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.0005 to 2% (weight/weight) azelastine.

3. A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

4. A method as set forth in claim 1 in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

5. A method as set forth in claim 1 in which the medicament contains a pharmaceutically usable preservative in an amount of 0.001 to 0.1%.

6. A method as set forth in claim 1 in which the medicament is a solution.

7. A method as set forth in claim 1 in which the medicament is an aqueous solution.

8. A method as set forth in claim 1 in which the medicament is a solution which contains 0.001 to 0.05% (weight/volume of solution) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1% (weight/volume of solution) of alkylbenzyldimethyl ammonium chloride.

9. A method as set forth in claim 1 in which the medicament is applied by spraying.

10. A method as set forth in claim 1 in which the medicament is applied as drops.

11. A method as set forth in claim 1 in which the medicament is a powder.

12. A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

* * * * *

# UNITED STATES PATENT AND TRADEMARK OFFICE
## CERTIFICATE EXTENDING PATENT TERM
## UNDER 35 U.S.C. § 156

| | | |
|---|---|---|
| PATENT NO. | : | 5,164,194 |
| ISSUED | : | November 17, 1992 |
| INVENTOR(S) | : | Helmut Hettche |
| PATENT OWNER | : | Asta Medica, AG |

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

349 days

from November 17, 2009, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 27th day of February 1998.

Bruce A. Lehman

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and

# EXHIBIT 3

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT Application of

Helmut HETTCHE

Serial No. 07/551,644 Group Art Unit: 152

Filed: July 12, 1990 Examiner: L. Piccone

For: AZELASTINE-CONTAINING MEDICAMENTS

June 17, 1991

* * * * *



Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

Responsive to the Office Action dated January 25, 1991, please amend the above-identified application as follows:

IN THE CLAIMS:

Rewrite claims 1-4 and 12 as follows:

1. (amended) A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eye a medicament which contains a member [of] selected from the group consisting of azelastine and its physiologically acceptable salts.

2. (amended) A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.0005 to 2% (weight/weight) azelastine.

3. (amended) A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

4 (amended) A method as set forth in claim 1 in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

12. (amended) A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member [of] selected from the group consisting of azelastine and its physiologically acceptable salts.

REMARKS

The applicant respectfully requests reconsideration.

The claims have been amended in several respects to deal with the rejections under 35 U.S.C. 112. Thus, for example, the language introducing the Markush groups in claims 1 and 12 has been changed to the form suggested by the Examiner. In claims 2-4, the amounts of the physiologically acceptable salts has been described. This amendment is based on the disclosure on page 5, lines 6-8 from the bottom.

However, applicants submit that the phrase "predetermined amount" in claim 15 is not indefinite. The precise amount which is released when the atomizing container is actuated, of course, depends on two factors. First, it depends on the concentration of azelastine in the liquid in the aerosol container. Secondly, it depends on the amount of liquid which is released when the aerosol container is actuated. The two factors are selected so that the patient receives the dosage which is desired. The word

"predetermined" in this case does not imply any particular amount of liquid. Rather, it indicates that the aerosol container is one which releases a fairly precise amount each time it is actuated, so that the patient receives a desired amount.

In claim 18, it is thought that the conventional pharmaceutical carrier substances are known and need not be defined precisely. In this case, the active ingredient, azelastine, is put up in a powder. The kinds of inert components which are used to produce a pharmaceutical powder are known. While the terminology is broad, it is submitted that it is not indefinite.

Applicants respectfully traverse the rejection of claims 11 and 18 as lacking an enabling disclosure. The specification clearly teaches that it is possible to put up the claimed medicines in pharmaceutical powders. The concentration of active ingredient in the powders is disclosed at page 5, last three lines. The particle size is disclosed at page 10, lines 14-16. It is submitted that this provides sufficient information for a person skilled in the art to make the claimed compositions in the form of powders.

Applicant respectfully requests reconsideration of the rejection of claims 1, 6, 7, 9, 10, 11 and 12 as anticipated under 35 U.S.C. 102 over Vogelsang. These claims recite that azelastine is applied "directly to nasal tissues or to the conjunctival sac of the eye", and this process step is not disclosed in Vogelsang.

In discussing this ground of rejection on page 3 of the Office Action, the Examiner has not cited any portion of the reference which teaches this step. The comment that Vogelsang discloses the use of azelastine in a pharmaceutical

preparation that can be administered in usual embodiments such as tablets, etc. does not support an assertion that the reference discloses the specific form of administration claimed in this application, within the context of 35 U.S.C. 102. That provision of the patent statute is quite specific in requiring that the reference actually disclose the process which is claimed. A similar comment can be made with regard to the Examiner's contention that aerosol administration is disclosed in the reference, with the further comment that the reference does not disclose aerosol administration of azelastine (see discussion below).

The following are some of the legal authorities which define the scope of 35 U.S.C. 102.

> Ex parte Meyer, 213 USPQ 588, 590
>
> To anticipate a claimed invention, all limitations in the claims must be found in the reference since the claims measure the invention....Moreover, a rejection under 35 U.S.C. 102(e) necessarily implies that the invention is not new, i.e., that there is no difference between what is claimed and what is disclosed in the prior art. (Emphasis added.)
>
> Ex parte Stubbs, 149 USPQ 641
>
> Claims 7 and 8 are rejected as unpatentable over Jones et al. It is stated in the answer that this rejection is under 35 USC 102. However, it is apparent from the Examiner's position as to these claims that the rejection can only be under 35 U.S.C. 103 because the claims include a limitation that is not shown in the reference.
>
> In re Kalm, 154 USPQ 10
>
> A rejection under 35 U.S.C. 102(e)...necessarily implies that the invention sought to be patented has been described...that there are no differences between what is claimed and what is disclosed....

The reference simply does not disclose the step of administering azelastine "directly to nasal tissues or to the

conjunctival sac of the eye". Therefore, this ground of rejection is thought to be inappropriate.

Applicant also requests reconsideration of the rejection of the claims under 35 U.S.C. 103. Contrary to the Examiner's contention, it is submitted that Vogelsang does not disclose administering azelastine "directly to nasal tissues or to the conjunctival sac of the eye". The passages cited by the Examiner dd not establish the contrary.

Column 1, line 57 discloses a category of active ingredients which include azelastine, and, as the Examiner has said, azelastine is specifically exemplified in the patent. However, this particular passage does not say anything about the mode of administration.

Column 6, line 65 which the Examiner has cited discloses various dosage forms, but, again, there is no disclosure of direct administration to nasal or eye tissues. While treatment of disorders of the skin and mucus membranes are mentioned, direct administration to nasal tissues and the conjunctival sac of the eye are not mentioned.

The Examiner has also referred to the disclosure of an aerosol, but applicant submits that the Examiner has misunderstood this disclosure. The reference does not teach putting up azelastine in an aerosol. The aerosol is used to administer histamine in a guinea-pig test. The Examiner has referred to Column 6, line 21 which is the heading for Table I. It refers to Histaminolytical activity in the histamine aerosol test on guinea-pigs. This test is described in Column 5, lines 49-63. In that test, the guinea pigs inhale an aerosol of histamine. The test compounds, such as azelastine, are administered "subcutaneously or orally" (column 5, line 58). Therefore, the disclosure of

aerosols in this reference is wholly unrelated to the use of aerosols in connection with the present invention.

The invention provides numerous advantages associated with other forms of administration. These are discussed on pages 1 and 2 of the present application. The Examiner has pointed to the declarations submitted previously, but of course these are concerned with a comparison with a different reference. These declarations show that azelastine is more effective than other active agents disclosed in the Engel reference which was cited previously. However, since the Vogelsang reference actually discloses azelastine, it raises entirely different issues.

The only routes of administration actually disclosed in Vogelsang are subcutaeous (parenteral) and oral. There is no evidence that azelastine would be effective when applied directly to nasal tissues or to the eye. The advantages of the present invention relate to a different mode of administration, but there is no suggestion of them in this reference. This is reinforced by Examples 43-46 which relate to dosage units, i.e., tablets, dragees, suppositories and injection ampoules.

Finally, applicants request reconsideration of claims 13-17. The Examiner has shown that the various appliances covered by those claims are known and that they have been used to administer medications. There can be no doubt that these appliances are not broadly new as a way to administer medications. However, it is submitted that it would not have been obvious to put up azelastine in these kinds of appliances, because it was not obvious to administer azelastine to parts of the body for which these types of appliances are suited.

For these reasons, it is submitted that the present invention is patentable, and that all informalities in the claims have been corrected. Favorable reconsideration of the claims and allowance are respectfully requested.

Respectfully submitted,
CUSHMAN, DARBY & CUSHMAN

By _____
Lawrence A. Hymo
Reg. No. 19,037

1615 L Street N.W.
Washington, D.C. 20036

Telephone (202) 861-3000

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RECEIVED
MAY 0 8 1992
GROUP 150

In re PATENT Application of

Helmut HETTCHE

Serial No. 07/551,664 Group Art Unit: 152

Filed: July 12, 1992 Examiner: L. Piccone

For: AZELASTINE-CONTAINING MEDICAMENTS

B/EXT ①
+
Brief

April 28, 1992

BRIEF FOR THE APPLICANT

Dell
5/11/92

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

This is an appeal from the final rejection of claims 1-12 and 18.

STATUS OF CLAIMS

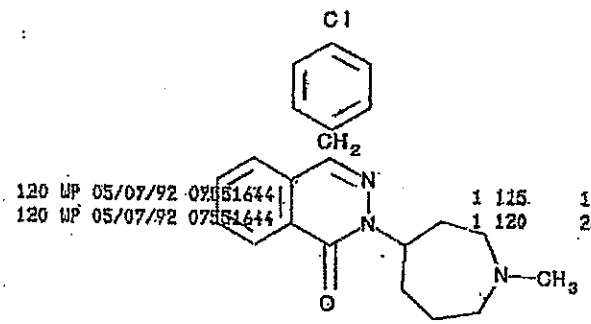
The application originally contained claims 1-18. Claims 13-17 have been cancelled, leaving claims 1-12 and 18, which are presented in this appeal.

STATUS OF AMENDMENTS

An amendment was submitted after the final rejection, cancelling claims 13-17. It has been entered.

SUMMARY OF THE INVENTION

The invention relates to a new use of azelastine, a phthalazinone derivative having the formula:




120 UP 05/07/92 07551644 1 115 110.00 CK
120 UP 05/07/92 07551644 1 120 260.00 CK

MP0112

Azelastine has been used in prophylactic treatment of asthma and for its anti-allergic and antihistamine properties.

The present invention is based on a surprising discovery that azelastine and its physiologically acceptable salts display advantageous and surprising effects when applied directly in the nose and/or to the conjunctival sac of the eye. This treatment produces elimination or marked relief in allergy-related rhinitis, the common cold, and vasomotor cold. Further, application directly in the nose has been found to have advantageous effects on the mucous membrane of the eye.

The invention is claimed in claim 1 as a method which comprises *applying* azelastine *directly to the nasal tissues or to the conjunctival sac of the eye.* Claims 2-8 relate to more preferred features of the pharmaceutical composition containing azelastine which is applied in accordance with the method of claim 1. Claims 9-11 relate to more preferred modes of application of the azelastine-containing composition. Claim 12 is similar to claim 1, in defining a method of treatment with azelastine. However, it defines the symptoms which are treated more specifically than in claim 1, i.e., "a patient suffering from allergy-related or vasomotor or rhino virus-related colds or symptoms."

Claim 18 relates to a novel composition containing azelastine which is useful for the present invention. More specifically, Claim 18 relates to a powder containing azelastine and an appropriate pharmaceutical solid carrier.

ISSUES

The Examiner has rejected claims 1-12 and 18 as obvious under 35 U.S.C. § 103 over Vogelsang, U.S. Patent 3,813,384 "in view of art admitted in the specification." The Examiner separately rejected claims 13-17. However, since those claims have been cancelled, it is assumed that the

grounds of rejection applied against those claims are no longer at issue.

GROUPING OF CLAIMS

The Examiner has grouped claims 1-12 and 18 together. However, applicants believe that claims 1-12 should be considered separately from claim 18.

ARGUMENT

Claims 1-12 and 18 stand rejected as obvious from the disclosure of the cited Vogelsang, et al. patent in view of "the art admitted in the specification." The claims relate to administration of azelastine directly into nasal and eye tissues.

It is not clear what aspects of the art admitted in the specification is the basis of the examiner's reference, but the introductory passage on page 1 simply mentions to the fact that azelastine has anti-allergic and anti-histamine properties. This information does not imply a mode of administration, although, as shown below, the customary mode of administration for such medications is systemic (e.g., oral or injection). Further, as the cited Vogelsang patent refers to the fact that its compounds are used for the treatment of histamine induced disturbances (see Abstract, Column 1) and allergies (Column 6, line 72), it is not seen where the above cited passage adds anything to the disclosure of the Vogelsang patent. The Examiner has referred on page 3 of the Office Action to the use of "preseruähres" (sic) in this connection, but this comment is not understood. Therefore, it is the disclosure of the Vogelsang patent which is the focus of the following remarks.

In his discussion of this patent, on page 3 of the Final Rejection, the Examiner has referred to column 43 lines 5-15 of Vogelsang, but this comment also is not understood. There is no column 43 in this patent.

The only information in the Vogelsang patent on mode of administration is in the paragraph bridging columns 6 and 7, viz.

> The compounds according to the present invention are used as active ingredients in pharmaceutical preparations and may be administered in *usual embodiments such as tablets, dragees, capsules, suppositories, drops, ointments, creams as well as injection solutions*. They are in particular used for the treatment of the various forms of allergies. Thus, they have been used successfully in humans in the treatment of asthma bronchiale, for the treatment of various disorders of the skin and mucous membranes hay fever and rhinitis vasmotorica. In general, they are administered in such treatments in a dosage of 0.4 to 4 mg. per day and human patient. The symptoms of the above allergic diseases may be effectively reduced upon a single dose for up to 24 hours. The effectiveness of the components of the present invention in humans which is produced very rapidly and over a prolonged period of time in comparison to other antihistamines, may be particularly well shown in the reduction of the size of an artificially produced lesion by means of a histamine liberator according to L. Kerp, H. Kasimiar, P.N. Tie, Med. Welt 17 NF 2794 (1966). The compounds according to the present invention may be used as such or in combination with other active ingredients as they are usual in antihistaminic preparations.

The portion which has been shown in italics above appears to be the sole basis for the rejection, and more particularly the disclosure that the compounds "may be administered in...drops..." To this, the Examiner has added the following comment:

> It would have been obvious to administer the azelastine composition of Vogelsang directly to the nasal tissues or conjunctival sac...because these are the areas to which medicament drops are normally applied.

However, the Examiner has indulged in a leap of logic which is not supported by the reference in making this comment. The reference does not say that drops are administered to the patient. It merely says that the compounds may be administered in drops. Thus, a medicine dropper is a

well known device for measuring liquids. See for example page 1329 in the attached extract from *The United States Pharmacopoeia* which describes the use of a medicine dropper and its ability to deliver a measured quantity of liquid, with various degrees of precision. But there is no indication of where the drops are to be delivered. For example, a medicine dropper is used as a means of delivering a measured quantity of a concentrated liquid to water which is to be swallowed or used as a mouthwash.

The Examiner has cited no reference to support his contention that "the nasal tissues or conjunctival sac...are the areas to which medicament drops are normally applied." However, such a sweeping statement, which provides the sole link between the Vogelsang patent and the present invention, should be supported by a reference.

Referring again to the attached extract from *The United States Pharmacopoeia*, it will be noted that various modes of administration are discussed. Compositions which are intended to be administered to the nose are referred to as "Nasal Solutions" and compounds which are administered to the eye are referred to as "Ophthalmic Solutions", see pages 1655 and 1338. On the other hand, among the forms of medicine which are described, the word "drops" does not appear as a form of material to be administered to the eyes or nasal passages.

Similarly, the words "ointment" and "cremes" are used in the reference, and these are mentioned in the attached copy of an extract from Remington's *Pharmaceutical Sciences*. See pages 1594 and 1616. However, there is no indication of direct application to nasal passages and eyes.

Finally, there is attached a copy of an extract from *Drug Facts and Comparisons*. While numerous antihistamines are mentioned, and modes of administration are described, there is no suggestion of direct application to the eyes and

nasal passages. Dosage forms such as capsules, tablets, injections, suppositories, elixirs and syrups are described, but none for direct application to the eyes and nasal passages.

Therefore, the only link between the present invention and the cited Vogelsang reference is the Examiner's interpretation of the word "drops" in this patent, and the Examiner's unsubstantiated comment that "the nasal tissues or conjunctival sac...are the areas to which medicament drops are normally applied." However, as indicated above, such a sweeping statement, providing the sole link between the reference and the present invention and the cited patent, ought to be supported by a reference. Since none has been cited, it is submitted that the claims should be allowed.

Further, applicant requests that the Board consider the decision in the case of *Ex parte Keith*, 154 USPQ 320, which held:

> Asserted inherency must be a necessary result and not merely a possible result. Ex parte Vander Wal et al., 705 O.G. 5, 1956 USPQ 11, 109 USPQ 119, and decisions cited therein.

Here, the Examiner reasons that the only possible meaning of the reference to "drops" in the reference is that they are to be applied directly to the eyes and nasal passages. However, the Examiner has not shown, by citation of a reference, or in any other way, that this is the only possible meaning of the word "drops." Rather, a medicine dropper is simply a device for measuring a liquid. While droppers are used to administer liquid medications to eyes and nasal passages, this does not mean that this mode of administration is the "necessary" and only "possible" inference to be drawn from the reference to "drops" in the cited patent.

The foregoing comments are applicable to both claims 1-12 and claim 18. However, the following additional com-

ments are thought to be appropriate specifically to claim 18.

Claim 18 relates to a powder containing azelastine and a pharmaceutical carrier. Powders are not among the materials mentioned in the cited Vogelsang patent, and so this claim is clearly patentable.

CONCLUSION

For these reasons, it is submitted that the claims are patentable and that they should be allowed.

Respectfully submitted,
CUSHMAN, DARBY & CUSHMAN

By _____
Lawrence A. Hymo
Reg. No. 19,057

1615 L Street N.W.
Washington, D.C. 20036
Tel. (202) 861-3015

APPENDIX

THE CLAIMS

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

2. A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.0005 to 2% (weight/weight) azelastine.

3. A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

4. A method as set forth in claim 1 in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

5. A method as set forth in claim 1 in which the medicament contains a pharmaceutically usable preservative in an amount of 0.001 to 0.1%.

6. A method as set forth in claim 1 in which the medicament is a solution.

7 A method as set forth in claim 1 in which the medicament is an aqueous solution.

8. A method as set forth in claim 1 in which the medicament is a solution which contains 0.001 to 0.05% (weight/volume of solution) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1%

(weight/volume of solution) of alkylbenzyldimethyl ammonium chloride.

9. A method as set forth in claim 1 in which the medicament is applied by spraying.

10. A method as set forth in claim 1 in which the medicament is applied as drops.

11. A method as set forth in claim 1 in which the medicament is a powder.

12. A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

18. Powder containing 0.0005 to 2% of azelastine or a physiologically acceptable salt of azelastine as active agent together with conventional pharmaceutical carrier substances.

# EXHIBIT 4

# BLACK'S MEDICAL DICTIONARY

Edited by C. W. H. Havard, MA, DM, FRCP

Thirty-fifth edition

BARNES & NOBLE BOOKS
TOTOWA, NEW JERSEY

Black's medical dictionary.—35th ed.
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I. Havard, C.W.H.
610'.3'21 R125

ISBN 0-7136-2810-3

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35 Bedford Row London WC1R 4JH



In its earlier editions *Black's Medical Dictionary* was edited by:
J. D. Comrie, MD – first to seventeenth editions, 1906–42
H. A. Clegg, FRCP – eighteenth edition, 1944
W. A. R. Thomson, MD – nineteenth to thirty-fourth editions, 1948–84

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**PHTHIRIASIS** means the condition of eczema, matted hair, dirt, and enlarged glands caused by the crab louse (*Pediculus pubis*). (See PEDICULOSIS.)

**PHTHISIS** means wasting, and is the general term applied to that progressive enfeeblement and loss of weight that arise from tuberculous disease of all kinds, but especially from the disease as it affects the lungs.

**PHYSIOLOGY** is the branch of medical science that deals with the healthy functions of different organs, and the changes that the whole body undergoes in the course of its activities.

**PHYSIOTHERAPY** is the form of treatment involving the use of physical measures, such as exercise, heat and massage in the treatment of disease. An alternative name is PHYSICAL MEDICINE.

**PHYSOSTIGMINE**, or ESERINE, is an alkaloid obtained from Calabar bean, the seed of *Physostigma venenosum*, a climbing plant of West Africa. Calabar bean is known also as the ordeal bean, because preparations derived from it were at one time used by the natives of West Africa to decide the guilt or innocence of accused persons, the guilty being supposed to succumb to its action, while the innocent escaped. Its action depends on the presence of two alkaloids, the one known as physostigmine or eserine, the other as calabarine, the former of these being much the more important.
**Action:** Physostigmine produces the same effect as stimulation of the parasympathetic nervous system (qv): ie, it constricts the pupil, stimulates the gut, increases the secretion of saliva, stimulates the bladder, and increases the irritability of voluntary muscle. In poisonous doses it brings on a general paralysis.
**Uses:** It is used in medicine in the form of physostigmine salicylate. Its main use is to contract the pupil and thereby reduce the pressure inside the eyeball. For this purpose it is used as eye-drops or as lamellae. It is also given by subcutaneous injection to stimulate the gut when this is paralysed or atonic. It is the specific antidote (qv) to atropine and is therefore used in the treatment of atropine poisoning (qv).

**PHYTOMENADIONE** is the *British Pharmacopoeia* name for vitamin K. (See VITAMIN.)

**PIA MATER** is the membrane closely investing the brain and spinal cord, in which run blood-vessels for the nourishment of these organs. (See BRAIN; SPINAL CORD.)

**PICA** (Latin for magpie) is a term which means an abnormal craving for unusual foods. It is not uncommon in pregnancy. Among the unusual substances for which pregnant women have developed a craving are soap, clay pipes, bed linen, charcoal, ashes — and almost every imaginable foodstuff taken in excess. In primitive races it is taken to mean that it indicates the growing foetus requires such food. It is also not uncommon in children. (See APPETITE; LEAD POISONING.)

**PICORNAVIRUSES** derive their name from pico (small) and RNA (because they contain ribonuleic acid). They are a group of viruses which includes the enteroviruses (qv) and the rhinoviruses (qv).

**PICRIC ACID**, or TRINITROPHENOL, is used for preparing explosives, and so is employed in medicine only in solution. As it coagulates albumin, it produces a soothing pellicle over any raw surface with which it is brought into contact. It has antiseptic properties, but is rapidly going out of use because of its toxic effects.

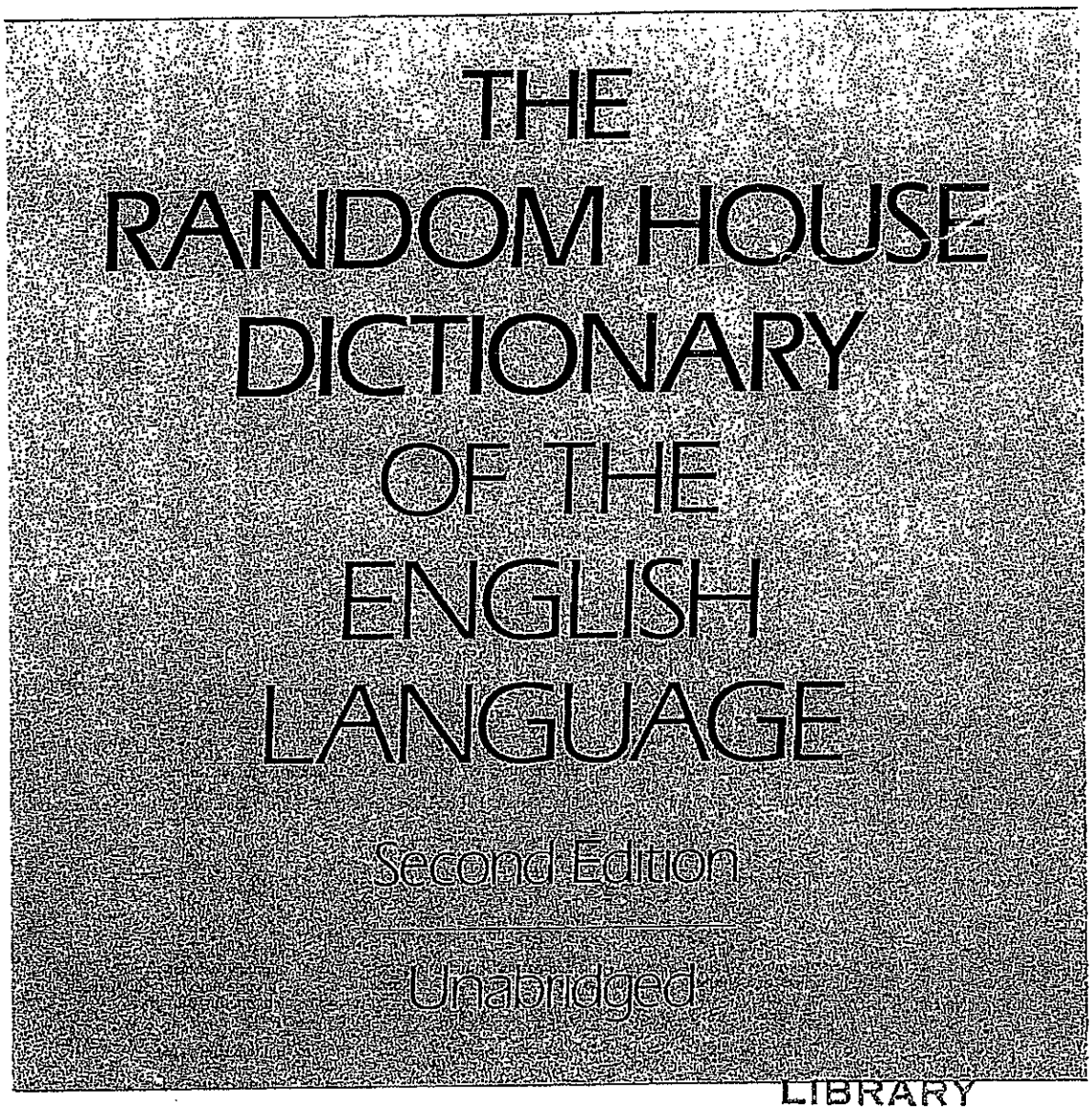
**PIGEON BREAST** (see CHEST DEFORMITIES).

**PIGEON-BREEDER'S LUNG**, or BIRD FANCIER'S LUNG as it is sometimes known, is a form of extrinsic allergic alveolitis resulting from sensitization to pigeons. In pigeon fanciers skin tests have revealed sensitization to pigeons' droppings, eggs, protein and serum, even though there has been no evidence of any illness. (See ALVEOLITIS.)

**PIGMENT** is the term applied to the colouring matter of various secretions, blood, etc.; also to any medicinal preparation of thick consistence intended for painting on the skin or mucous membranes.

**PILES**, or HAEMORRHOIDS, consist of a varicose and often inflamed condition of the veins about the lower end of the bowel, known as the haemorrhoidal veins.
**Varieties:** It is usual to divide haemorrhoids into external piles, internal piles, and mixed piles. To understand this division, it is important to remember that at the margin of the anus the skin joins the mucous membrane of the bowel in a sharp line, and that the bowel is kept closed by two circular muscles, the external sphincter and internal sphincter. The external sphincter is a weak muscle situated immediately beneath the skin, while the internal sphincter is a stronger circular band, extending up the bowel for about 2½ cm. External piles are found outside the bowel, and are covered by skin, being brown or dusky purple in colour; internal piles are within the opening, covered by mucous membrane, and are bright red or cherry-coloured. Mixed piles are those situated just on the margin, and covered half by skin, half by mucous membrane. Even internal piles do not extend past the position of the internal sphincter muscle.
**Causes:** There is always a tendency for the veins in this situation to become distended, partly because they are unprovided with

# EXHIBIT 5



*Dedicated to the memory of*
*Jess Stein*





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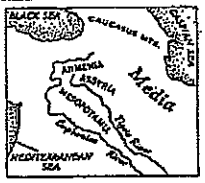
[1635–45; < LL (grammar sense only). n. use of fem. sing. of L *medius* central. MID¹]

**Me·di·a** (mē′dē ə), *n.* an ancient country in W Asia, S of the Caspian Sea, corresponding generally to NW Iran. *Cap.:* Ecbatana




**Mo′dia Atropate′ne,** an ancient region in NW Iran, formerly a part of Media. Also called **Atropatene.**

**mo′dia con′tor,** a library, usually in school, that contains and encourages the use of audiovisual media and associated equipment as well as books, periodicals, and the like.

**me·di·a·cy** (mē′dē ə sē), *n.* the state of being mediate. [1375–1425; late ME: intercession; see MEDIATE, -ACY]

**mē·di·ad** (mē′dē ad′), *adv. Anat., Zool.* toward the middle line or plane. [1876–80; MEDI- + L *ad* to, toward]

**me·di·ae·val** (mē′dē ē′vəl, mid′ē-, mid ē′vəl), *adj.* medieval.

**me′dia event′,** a celebration, stunt, spectacle, or other activity carefully orchestrated to attract the attention of the news media. [1970–75]

**me·di·a·gen·ic** (mē′dē ə jen′ik), *adj.* having qualities or characteristics that are especially appealing or attractive when presented in the mass media: *a mediagenic politician.* [1970–75; MEDIA¹ + -GENIC]

**me·di·al** (mē′dē əl), *adj.* 1. situated in or pertaining to the middle; median; intermediate. 2. pertaining to a mean or average; average. 3. ordinary. 4. *Phonet.* within a word or syllable; neither initial nor final, as the *t, a,* and *n* in *stand.* 5. *Entomol.* pertaining to, involving, or situated near the media. —*n.* 6. *Phonet.* a. a medial sound or letter. b. media² (def. 1). [1560–70; < LL *medialis* middle. See MEDIUM, -AL¹] —**me′di·al·ly,** *adv.*

**me′dial mo′raine′,** a ridge of glacial drift formed by the junction of two converging valley glaciers.

**me·di·an** (mē′dē ən), *adj.* 1. acting or pertaining to a plane dividing something into two equal parts, esp. one dividing an animal into right and left halves. 2. situated in or pertaining to the middle; medial. —*n.* 3. *Arith., Statistics.* the middle number in a given sequence of numbers, taken as the average of the two middle numbers when the sequence has an even number of numbers: *4 is the median of 1, 3, 4, 8, 9.* 4. *Geom.* a straight line from a vertex of a triangle to the midpoint of the opposite side. 5. Also called **midpoint.** a vertical line that divides a histogram into two equal parts. Cf. **central tendency.** 6. See **median strip.** [1535–45; < L *medianus* in the middle. See MEDIUM, -AN] —**me′di·an·ly,** *adv.*

**Mē·di·an** (mē′dē ən), *adj.* 1. of or pertaining to Media, the Medes, or their language. —*n.* 2. a Mede. 3. the Iranian language of ancient Media, contemporaneous with Old Persian. [1595–1605; MEDI(A) + -AN]

**me′dian le′thal dose′,** the quantity of a lethal substance, as a poison or pathogen, or of ionizing radiation that will kill 50 percent of the organisms subjected to it in a specified time period. *Symbol:* $LD_{50}$ [1946–50]

**me′dian plane′,** *Anat.* a vertical plane that divides an organism into symmetrical halves.

**me′dian point′,** *Geom.* centroid (def. 2).

**me′dian strip′,** a paved, planted, or landscaped strip in the center of a highway that separates lanes of traffic going in opposite directions. Also called **me′dial strip′, median.** [1945–50]

**mē·di·ant** (mē′dē ənt), *n.* the third degree of a major or minor musical scale. [1720–30; < It *mediante* < LL *mediant-* (s. of *mediāns,* prp. of *mediāre* to be in the middle. See MEDIUM, -ANT]

**mē·di·as·ti·num** (mē′dē ə stī′nəm), *n., pl.* **-as·ti·na** (-ə stī′nə). *Anat.* 1. a median septum or partition between two parts of an organ, or paired cavities of the body. 2. the partition separating the right and left thoracic cavities, formed of the two inner pleural walls, and, in humans, comprising all the viscera of the thorax except the lungs. [1535–45; < NL; cf. *mediastinus* of middle class, upper. identical with L *mediastin(us)* a low-ranking slave, perh. deriv. of *medius* MID¹, though sense and formation unclear] —**mē′di·as·ti′nal,** *adj.*

**mē·di·ate** (*v.* mē′dē āt′; *adj.* mē′dē it), *v.,* **-at·ed, -at·ing,** *adj.* —*v.t.* 1. to settle (disputes, strikes, etc.) as an intermediary between parties; reconcile. 2. to bring about (an agreement, accord, truce, peace, etc.) as an intermediary between parties by compromise, reconciliation, removal of misunderstanding, etc. 3. to effect (a result) or convey (a message, gift, etc.) by or as if by an intermediary. —*v.i.* 4. to act between parties to effect an agreement, compromise, reconciliation, etc. 5. to occupy an intermediate place or position. —*adj.* 6. acting through, dependent on, or involving an intermediate agency; not direct or immediate. [1375–1425; late ME < LL *mediātus,* ptp. of *mediāre* to be in the middle, intercede. See MEDIUM, -ATE¹] —**mē′di·ate·ly,** *adv.* —**mē′di·ate·ness,** *n.*

—**Syn.** 1, 2. arbitrate. 4. intercede, interpose

**mē′diated generaliza′tion,** *Psychol.* generalization (def. 4c).

**mē·di·a·tion** (mē′dē ā′shən), *n.* 1. action in mediating between parties, as to effect an agreement or reconciliation. 2. *Internat. Law.* an attempt to effect a peaceful settlement between disputing nations through the friendly good offices of another power. [1350–1400; ME < ML *mediātiōn-* (s. of *mediātiō*). See MEDIATE, -ION]

—**Syn.** 1. MEDIATION, ARBITRATION designate processes for bringing about agreement or reconciliation between opponents in a dispute. MEDIATION implies deliberation that results in solutions that may or may not be accepted by the contending parties. ARBITRATION involves a more formal deliberation, it being understood that the results will be binding on the contending parties.

**mē·di·a·tive** (mē′dē ā′tiv, -ə tiv), *adj.* mediating; mediatory. [1805–15; MEDIATE + -IVE]

**mē·di·a·tize** (mē′dē ə tīz′), *v.t.,* **-tized, -tiz·ing.** to annex (a principality) to another state, while allowing certain rights to its former sovereign. Also, *esp. Brit.,* **mē′di·a·tise′.** [1820–30; MEDIATE + -IZE, modeled on G *mediatisieren*] —**mē′di·a·ti·za′tion,** *n.*

**mē·di·a·tor** (mē′dē ā′tər), *n.* a person who mediates, esp. between parties at variance. [1250–1300; < LL (see MEDIATE, -TOR); r. ME *mediatour* < AF < LL, as above] —**mē′di·a·tor·ship′,** *n.*

**mē·di·a·to·ri·al** (mē′dē ə tôr′ē əl, -tōr′-), *adj.* of, pertaining to, or characteristic of a mediator. [1640–50; MEDIATORY + -AL¹]

**mē·di·a·to·ry** (mē′dē ə tôr′ē, -tōr′ē), *adj.* 1. pertaining to mediation. 2. having the function of mediating. [1610–20; < LL *mediātōrius.* See MEDIATE, -TORY¹]

**mē·di·a·trix** (mē′dē ā′triks), *n., pl.* **-a·tri·ces** (-ə trī′sēz, -ā′tri sēz′), **-a·trix·es.** a woman who mediates, esp. between parties at variance. Also, **me·di·a·tress,** mē·di·a·trice (mē′dē ā′tris). [1625–75; late ME < LL *mediātrix,* fem. of *mediātor* MEDIATOR; see -TRIX] —**Usage.** See **-ess, -trix.**

**Med·i·bank** (med′ē bangk′), *n.* the national health-insurance program instituted in Australia. [MEDI(CAL) + BANK¹]

**med·ic**¹ (med′ik), *n.* 1. a member of a military medical corps; corpsman. 2. a doctor or intern. 3. a medical student. [1650–60; < L *medicus;* see MEDICAL]

**med·ic**² (med′ik), *n.* any plant belonging to the genus *Medicago,* of the legume family, having trifoliate leaves and grown as a forage crop. Also, **medick.** Cf. **alfalfa, bur clover.** [1400–50; late ME *medike* < L *medica* < Gk (pósa) *Mēdikḗ* lit., Median (grass)]

**med·i·ca·ble** (med′i kə bəl), *adj.* responsive to medical treatment; curable. [1610–20; < L *medicābilis* healing, curative. See MEDICAL, -ABLE] —**med′i·ca·bly,** *adv.*

**Med·i·caid** (med′i kād′), *n.* (*sometimes l.c.*) a U.S. government program, financed by federal, state, and local funds, of hospitalization and medical insurance for persons of all ages within certain income limits. Cf. **Medicare.** [MEDICAL) + AID]

**med·i·cal** (med′i kəl), *adj.* 1. of or pertaining to the science or practice of medicine: *medical history; medical treatment.* 2. curative; medicinal; therapeutic: *medical properties.* 3. pertaining to or requiring treatment by other than surgical means. 4. pertaining to or giving evidence of the state of one's health: *a medical discharge from the army; a medical examination.* —*n.* 5. something done or received in regard to the state of one's health, as a medical examination. [1640–50; < ML *medicālis,* equiv. to L *medic(us)* medical (adj.), physician (n.) (deriv. of *medērī* to heal; see -IC) + *-ālis* -AL¹] —**med′i·cal·ly,** *adv.*

**med′ical exam′iner,** 1. a physician or other person trained in medicine who is appointed by a city, county, or the like, to perform autopsies on the bodies of persons supposed to have died from unnatural causes and to investigate the cause and circumstances of such deaths. 2. a physician retained by an insurance company, industrial firm, or the like, to give medical examinations to its clients or employees. [1840–50]

**med·i·cal·ize** (med′i kə līz′), *v.t.,* **-ized, -iz·ing.** to handle or accept as deserving of or appropriate for medical treatment. Also, *esp. Brit.,* **med′i·cal·ise′.** [MEDICAL + -IZE] —**med′i·cal·i·za′tion,** *n.*

**med′ical jurispru′dence.** See **forensic medicine.** [1780–90]

**mē·dic·a·ment** (mə dik′ə mənt, med′i kə-), *n.* a healing substance; medicine; remedy. Also called **med·i·cant** (med′i kənt). [1535–45; < L *medicāmentum* remedy, physic, equiv. to *medicā(rī)* to cure + *-mentum* -MENT; See MEDICATE] —**med·i·ca·men·tal** (med′i kə men′tl), **med′i·ca·men′tous,** *adj.*

**Med·i·care** (med′i kâr′), *n.* 1. (*sometimes l.c.*) a U.S. government program of hospitalization insurance and voluntary medical insurance for persons aged 65 and over and for certain disabled persons under 65. Cf. **Medicaid.** 2. (*l.c.*) any of various government-funded programs to provide medical care to a population. [MEDI(CAL) + CARE]

**med·i·cate** (med′i kāt′), *v.t.,* **-cat·ed, -cat·ing.** 1. to treat with medicine or medicaments. 2. to impregnate with a medicine: *medicated cough drops; a medicated bandage.* [1615–25; < L *medicātus* medicated (ptp. of *medicāre*), healed (ptp. of *medērī*). See MEDICAL, -ATE¹]

**med·i·ca·tion** (med′i kā′shən), *n.* 1. the use or application of medicine. 2. a medicinal substance; medicament. [1375–1425; late ME < L *medicātiōn-* (s. of *medicātiō*). See MEDICATE, -ION]

**med·i·ca·tive** (med′i kə tiv), *adj.* medicinal. [1635–

**Me·di·ci** (med′i chē; *It.* me′dē chē), *n.* 1. Catherine de'. See **Catherine de Médicis.** 2. Cos·mo or Co·si·mo de' (kōz′mō or kō′zē mō dā), (*"the Elder"*), 1389–1464, Italian banker, statesman, and patron of art and literature. 3. Cosmo or Cosimo de' (*"the Great"*), 1519–74, duke of Florence and first grand duke of Tuscany. 4. Gio·van·ni de' (jō vän′nē dā). See **Leo X.** 5. Giu·lio de' (jōō′lyō dā). See **Clement VII.** 6. Lo·ren·zo de' (lō ren′tsō dā), (*"Lorenzo the Magnificent"*), 1449–92, poet and patron of the arts and literature; ruler of Florence 1478–92 (father of Leo X). 7. Ma·ri·a de' (mə rē′ə dā; *It.* mä rē′ä dā). See **Marie de Médicis.** —**Med·i·ce·an** (med′i sē′ən, -chē′ən), *adj.*

**me·dic·i·na·ble** (mə dis′ə nə bəl), *adj.* Archaic. medicinal. [1350–1400; ME < MF. See MEDICINE, -ABLE]

**me·dic·i·nal** (mə dis′ə nl), *adj.* 1. of, pertaining to, or having the properties of a medicine; curative; remedial: *medicinal properties; medicinal substances.* 2. unpalatable; disagreeable: a medicinal taste. [1350–50; ME < L *medicinālis.* See MEDICINE, -AL¹] —**me·dic′i·nal·ly,** *adv.*

**medic′inal leech′,** a bloodsucking leech, *Hirudo medicinalis,* of Europe, introduced into the northeastern U.S., usually green with brown stripes, up to 4 in. (10 cm) long: once used by physicians to bleed patients. [1885–90]

**med·i·cine** (med′ə sin or, esp. *Brit.,* med′sən), *n., v.,* **-cined, -cin·ing.** —*n.* 1. any substance or substances used in treating disease or illness; medicament; remedy. 2. the art or science of restoring or preserving health or due physical condition, as by means of drugs, surgical operations or appliances, or manipulations: often divided into medicine proper, surgery, and obstetrics. 3. the art or science of treating disease with drugs or curative substances, as distinguished from surgery and obstetrics. 4. the medical profession. 5. (among North American Indians) any object or practice regarded as having magical powers. 6. **give someone a dose or taste of his or her own medicine,** to repay or punish a person for an injury by use of the offender's own methods. 7. **take one's medicine,** to undergo or accept punishment, esp. deserved punishment: *He took his medicine like a man.* —*v.t.* 8. to administer medicine to. [1175–1225; ME *medicin* < L *medicina* (*ars*) healing (art), fem. of *medicinus* pertaining to a physician. See MEDICAL, -INE¹]

—**Syn.** 1. medication, drug; pharmaceutical; physic.

**med′icine ball′,** a large, solid, heavy, leather-covered ball, thrown from one person to another for exercise. [1890–95]

**Med′icine Bow′ Range′** (bō), a range of the Rocky Mountains, in Wyoming and Colorado. Highest peak: Medicine Bow Peak, 12,014 ft. (3662 m).

**med′icine dance′,** a ritual dance performed by some North American Indians to invoke supernatural assistance as for driving out disease. [1800–10]

**Med′icine Hat′,** a city in SE Alberta, in SW Canada. 32,811.

**med′icine lodge′,** 1. a structure used for various ceremonials of North American Indians. 2. (*caps.*) the most important religious society among the central Algonquian tribes of North America. [1800–10]

**med′icine man′;** 1. (among North American Indians and some other aboriginal peoples) a person believed to possess magical or supernatural powers; shaman. 2. a seller of patent medicine, esp. before 1900, presenting a medicine show to attract customers. [1795–1805]

**med′icine-show′,** a traveling troupe, esp. in the late 1800's, offering entertainment in order to attract customers for the patent medicines or purported cures proffered for sale. [1935–40, *Amer.*]

**medick** (med′ik), *n.* medic².

**med·i·co** (med′i kō′), *n., pl.* **-cos.** *Informal.* 1. a physician or surgeon; doctor. 2. a medical student. [1630–90; < Sp *médico,* It *medico* < L *medicus* physician; see MEDICAL]

**medico-,** a combining form representing **medical** in compound words: *medicolegal.* [comb. form repr. L *medicus* of, pertaining to healing; see MEDICAL]

**med·i·co-chi·rur·gi·cal** (med′i kō ki rûr′ji kəl), *adj.* 1. pertaining to medicine and surgery. 2. Archaic. consisting of both physicians and surgeons. [1800–10; MEDICO- + CHIRURGICAL]

**med·i·co-le·gal** (med′i kō lē′gəl), *adj.* pertaining to medicine and law or to forensic medicine. [1825–35; MEDICO- + LEGAL]

**me·di·e·val** (mē′dē ē′vəl, med′ē-, mid′ē-, mid ē′vəl), *adj.* 1. of, pertaining to, characteristic of, or in the style of the Middle Ages: *medieval architecture.* Cf. **Middle Ages.** 2. *Informal.* extremely old-fashioned; primitive. Also, **mediaeval.** [1820–30; < NL *medi(um)* ev(um) the middle age + -AL¹. See MEDIUM, AGE] —**me′di·e′val·ly,** *adv.*

**Me′di·e′val Greek′,** the Greek language of the Middle Ages, usually dated A.D. 700 to 1600. Abbr.: MGk, MGk., MGr. Also called **Middle Greek.**

**me·di·e·val·ism** (mē′dē ē′və liz′əm, med′ē-, mid′ē-, mid ē′və-), *n.* 1. the spirit, practices, or methods of the Middle Ages. 2. devotion to or adoption of medieval ideals or practices. 3. a medieval belief, practice, or the like. Also, **mediaevalism.** [1850–55; MEDIEVAL + -ISM]

**me·di·e·val·ist** (mē′dē ē′və list, med′ē-, mid′ē-, mid ē′vəl), *n.* 1. an expert in medieval history, literature, philosophy, etc. 2. a person who is greatly attracted to the art, culture, spirit, etc., of the Middle Ages. [1850–55; MEDIEVAL + -IST]

**Me′di·e′val Lat′in,** the Latin language of the literature of the Middle Ages, usually dated A.D. 700 to 1500, including many Latinized words from other languages. Abbr.: ML, M.L. Also called **Middle Latin.** [1880–85]

**med·i·gap** (med′i gap′), *n.* (*sometimes cap.*) private health insurance that supplements coverage for people already covered by government insurance. [MEDI(CAL) + GAP, on the model of MEDICARE]

CONCEPT ETYMOLOGY KEY: < , descended or borrowed from; >, whence; b, blend of, blended; c, cognate with; cf., compare; deriv., derivative; equiv., equivalent; imit., imitative; obs., obsolete; r., replacing; s., stem; sp., spelling, spelled; resp., respelling, respelled; trans., translation; ?, origin unknown; ", unattested; ± probably

# EXHIBIT 6

# McGraw-Hill Dictionary of CHEMICAL TERMS

Sybil P. Parker
EDITOR IN CHIEF

McGraw-Hill Book Company

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Auckland Bogotá Guatemala Hamburg
Lisbon London Madrid Mexico
Montreal New Delhi Panama Paris San Juan
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*On the cover:* Photomicrograph of potassium nitrate under high pressure, a specimen contained in a diamond-anvil high-pressure cell. (National Bureau of Standards)



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Consu

**apoatropine** $C_{17}H_{21}NO_2$ An alkaloid melting at 61°C with decomposition of the compound; highly toxic; obtained by dehydrating atropine.

**apple essence** *See* isoamyl valerate.

**apple oil** *See* isoamyl valerate.

**aprotic solvent** A solvent that does not yield or accept a proton.

**aqua** Latin for water.

**aqua ammonia** *See* ammonium hydroxide.

**aquafortis** *See* nitric acid.

**aquametry** Analytical processes to measure the water present in materials; methods include Karl Fischer titration, reactions with acid chlorides and anhydrides, oven drying, distillation, and chromatography.

**aqua regia** A fuming, highly corrosive, volatile liquid with a suffocating odor made by mixing 1 part concentrated nitric acid and 3 parts concentrated hydrochloric acid; reacts with all metals, including silver and gold. Also known as chloroazotic acid; chloronitrous acid; nitrohydrochloric acid; nitromuriatic acid.

**aquation** Formation of a complex that contains water by replacement of other coordinated groups in the complex.

**aqueous electron** *See* hydrated electron.

**aqueous solution** A solution with the solvent as water.

**aquo ion** Any ion containing one or more water molecules.

**Ar** *See* argon.

**arabite** *See* arabitol.

**arabitol** $CH_2OH(CHOH)_3CH_2OH$ An alcohol that is derived from arabinose; a sweet, colorless crystalline material present in D and L forms; soluble in water; melts at 103°C. Also known as arabite.

**arachic acid** *See* eicosanoic acid.

**arachidic acid** *See* eicosanoic acid.

**aralkyl** A radical in which an aryl group is substituted for an alkyl H atom. Derived from arylated alkyl.

**arbutin** $C_{12}H_{16}O_7$ A bitter glycoside from the bearberry and certain other plants; sometimes used as a urinary antiseptic.

**arc excitation** Use of electric-arc energy to move electrons into higher energy orbits.

**archen** *See* emodin.

**arc spectrum** The spectrum of a neutral atom, as opposed to that of a molecule or an ion; it is usually produced by vaporizing the substance in an electric arc; designated by the roman numeral I following the symbol for the element, for example, HeI.

**arecaidine methyl ester** *See* arecoline.

**arecoline** $C_8H_{13}O_2N$ An alkaloid from the betel nut; an oily, colorless liquid with a boiling point of 209°C; soluble in water, ethanol, and ether; combustible; used as a medicine. Also known as arecaidine methyl ester; methyl-1,2,5,6-tetrahydro-1-methylnicotinate.

**arene** *See* aromatic hydrocarbon.

**argentic** Relating to or containing silver.

**argentic oxide** *See* silver suboxide.

**elimination reaction** A chemical reaction involving elimination of some portion of a reactant compound, with the production of a second compound.

**ellagic acid** $C_{14}H_6O_8$ A compound isolated from tannins as yellow crystals that are minimally soluble in hot water. Also known as gallogen.

**eluant** A liquid used to extract one material from another, as in chromatography.

**eluate** The solution that results from the elution process.

**elution** The removal of adsorbed species from a porous bed or chromatographic column by means of a stream of liquid or gas.

**elutriation** *See* evigate.

**emanation** *See* radioactive emanation.

**emf** *See* electromotive force.

**emission flame photometry** A form of flame photometry in which a sample solution to be analyzed is aspirated into a hydrogen-oxygen or acetylene-oxygen flame; the line emission spectrum is formed, and the line or band of interest is isolated with a monochromator and its intensity measured photoelectrically.

**emission lines** Spectral lines resulting from emission of electromagnetic radiation by atoms, ions, or molecules during changes from excited states to states of lower energy.

**emission spectrometer** A spectrometer that measures percent concentrations of preselected elements in samples of metals and other materials; when the sample is vaporized by an electric spark or arc, the characteristic wavelengths of light emitted by each element are measured with a diffraction grating and an array of photodetectors.

**emission spectrum** Electromagnetic spectrum produced when radiations from any emitting source, excited by any of various forms of energy, are dispersed.

**emodin** $C_{14}H_4O_2(OH)_3CH_3$ Orange needles crystallizing from alcohol solution, melting point 256–257°C, practically insoluble in water, soluble in alcohol and aqueous alkali hydroxide solutions, occurs as the rhamnoside in plants such as rhubarb root and alder buckthorn; used as a laxative. Also known as archen; frangula emodin; frangulic acid; rheum emodin.

**empirical formula** A chemical formula indicating the variety and relative proportions of the atoms in a molecule but not showing the manner in which they are linked together.

**emulsification** The process of dispersing one liquid in a second immiscible liquid; the largest group of emulsifying agents are soaps, detergents, and other compounds, whose basic structure is a paraffin chain terminating in a polar group.

**emulsion** A stable dispersion of one liquid in a second immiscible liquid, such as milk (oil dispersed in water).

**emulsion breaking** In an emulsion, the combined sedimentation and coalescence of emulsified drops of the dispersed phase so that they will settle out of the carrier liquid; can be accomplished mechanically (in settlers, cyclones, or centrifuges) with or without the aid of chemical additives to increase the surface tension of the droplets.

**emulsion polymerization** A polymerization reaction that occurs in one phase of an emulsion.

**enallachrome** *See* esculin.

**enantiomer** *See* enantiomorph.

**solidus** In a constitution or equilibrium diagram, the locus of points representing the temperature below which the various compositions finish freezing on cooling, or begin to melt on heating.

**solidus curve** A curve on the phase diagram of a system with two components which represents the equilibrium between the liquid phase and the solid phase.

**solliquid** A system in which solid particles are dispersed in a liquid.

**solubility** The ability of a substance to form a solution with another substance.

**solubility coefficient** The volume of a gas that can be dissolved by a unit volume of solvent at a specified pressure and temperature.

**solubility curve** A graph showing the concentration of a substance in its saturated solution in a solvent as a function of temperature.

**solubility product constant** A type of simplified equilibrium constant, $K_{sp}$, defined for and useful for equilibria between solids and their respective ions in solution; for example, the equilibrium

$$AgCl(s) \rightleftarrows Ag^+ + Cl^-, \quad [Ag^+][Cl^-] = K_{sp}$$

where $[Ag^+]$ and $[Cl^-]$ are molar concentrations of silver ions and chloride ions.

**solubility test** 1. A test for the degree of solubility of asphalts and other bituminous materials in solvents, such as carbon tetrachloride, carbon disulfide, or petroleum ether. 2. Any test made to show the solubility of one material in another (such as liquid-liquid, solid-liquid, gas-liquid, or solid-solid).

**soluble** Capable of being dissolved.

**soluble barbital** *See* sodium barbital.

**soluble glass** *See* sodium silicate.

**soluble glusIde** *See* sodium saccharine.

**soluble guncotton** *See* pyroxylin.

**soluble indigo blue** *See* indigo carmine.

**soluble nitrocellulose** *See* pyroxylin.

**soluble saccharin** *See* sodium saccharin.

**solute** The substance dissolved in a solvent.

**solution** A single, homogeneous liquid, solid, or gas phase that is a mixture in which the components (liquid, gas, solid, or combinations thereof) are uniformly distributed throughout the mixture.

**solution pressure** 1. A measure of the tendency of molecules or atoms to cross a bounding surface between phases and to enter into a solution. 2. A measure of the tendency of hydrogen, metals, and certain nonmetals to pass into solution as ions.

**solutrope** A ternary mixture with two liquid phases and a third component distributed between the phases, or selectively dissolved in one or the other of the phases; analogous to an azeotrope.

**solvation** The process of swelling, gelling, or dissolving of a material by a solvent; for resins, the solvent can be a plasticizer.

**solvent** That part of a solution that is present in the largest amount, or the compound that is normally liquid in the pure state (as for solutions of solids or gases in liquids).

**solvolysis** A reaction in which a solvent reacts with the solute to form a new substance.

EXHIBIT 7

GRANT & HACKH'S

# CHEMICAL DICTIONARY

[American, International, European and British Usage]

*Containing the Words Generally Used in Chemistry, and Many of the Terms Used in the Related Sciences of Physics, Medicine, Engineering, Biology, Pharmacy, Astrophysics, Agriculture, Mineralogy, etc.*

*Based on Recent Scientific Literature*

FIFTH EDITION
*Completely Revised and Edited by*

**ROGER GRANT**

*M.A., D. de l'U., Ph.D., C. Chem., M.R.S.C.* *Consultant*

**CLAIRE GRANT**

*M.B., B.S., M.R.C.P.E.* *Medical Practitioner*

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The previous edition of this book was *Hackh's Chemical Dictionary*, 4th ed., published by McGraw-Hill in 1969. It was prepared by Dr. Julius Grant from a *Chemical Dictionary* compiled by Ingo W. D. Hackh. The current, or 5th, edition of this book was prepared by Dr. Roger L. Grant, whose father prepared the 4th edition.

*The editors for this book were Betty J. Sun and Susan Thomas, the designer was Naomi Auerbach, and the production supervisor was Teresa F. Leaden. It was set in Palatino by University Graphics, Inc.*

*Printed and bound by R. R. Donnelley & Sons Company.*

**mipor** Microporous. **m. rubber** A soft rubber, with pores of about 0.0004 mm average diameter. **m. scheider** A diaphragm of m. rubber used in accumulators
**mirabilite** $Na_2SO_4 \cdot H_2O$. A native sulfate.
**miramint** A tungsten-molybdenum alloy, used in cutting tools.
**mirbane oil** Nitrobenzene*
**Mirlon** Trademark for a synthetic polyamide fiber.
**mirror** A highly polished surface that reflects light; made of polished metal or glass. **concave ~** A )-shaped mirror. **convex ~** A (-shaped mirror. **plane ~** A flat mirror.
**mirrorstone** (1) Mica (2) Muscovite.
**MIS** Management information system.
**misce** Latin for "mix."
**mischmetal** (1) A mixture of rare-earth metals. (2) Commercial cerium (40–75% Ce) with La, Nd, Pr, etc., and sometimes 1–5% Fe; used for pyrophoric alloys. Cf. *Auer metal*.
**mischzinn** (German: "mixed tin") The alloy Sn 54.4, Pb 41.9, Sb 3.6%; used to prepare solders.
**miscibility** The ability of certain liquids to mix in all proportions. **m. gap** The temperature range in which certain normally miscible liquids will not mix.
**miscible** Capable of mixing or dissolving in all proportions. **im~** Not able to mix.
**miso** An edible fermented soybean paste. Cf. *kogi*.
**mispickel** $FeS_2 \cdot FeAs_2$. A native iron ore.
**Mississippian** See *geologic eras*, Table 38.
**mist** (1) Fog. Cf. *colloidal systems*. (2) Pharmaceutical abbreviation for mixture.
**mistletoe** The leaves and young twigs of *Pharadendron flavescens*; an antispasmodic and narcotic. Cf. *viscum*.
**mistura** Mist. Latin for "mixture"; used in pharmacy.
**Mitchell, Peter Dennis** (1920– ) British chemist. Nobel prize winner (1978), noted for work on chemiosmotic reactions
**mitochiondrion** A double-membrane structure in the living cell, which plays a role in the chemical changes involved in respiration.
**mitosis** Division of somatic cells, as part of cell regeneration and growth. The number of chromosomes remains the same. See *diploid, karyokinesis*. Cf. *meiosis*.
**mitragynine** $C_{23}H_{30}O_4N_2$ = 398.5. Mitragyne. An alkaloid, m.106, from *Mitragyna speciosa* (Rubiaceae).
**Mitscherlich** M., Ellhardt (1794–1863) German chemist. **M. desiccator** A desiccator, with side tubes for evacuation. **M. eudiometer** A closed glass buret, with platinum electrodes at one end and a glass stopcock at the other. **M. law** (1) The law of *isomorphism*, q.v., which is not rigidly correct: The same number of atoms of similar elements combined in the same way produce an identical crystalline structure. (2) The spectra of isomorphous substances are similar.
**mitsubuene** $C_{15}H_{24}$ = 204.4. A sesquiterpene for *Cryptotaenia japonica*, mitsuba-zeri (Umbelliferae), Japan.
**mix** (1) To intermingle. (2) A physical mixture of substances, applied to rubber, etc.
**mixed** **m. crystal** A crystal of 2 isomorphous substances, which crystallize in the same system. **m. ester** An ester R—COO—R′, in which the 2 radicals, R and R′, are different. **m. ether** An R—O—R′ ether, in which the radicals, R and R′, are different. **m. infection** The invasion by and growth of 2 or more microorganisms in the animal body. **m. ketones** A ketone of the type R—CO—R′. **m. salt** A salt derived from a polyvalent acid, in which the H atoms are replaced by different metals, as $KNaNH_4PO_4$.
**mixer** Equipment for incorporating one or more materials into another; a steel bowl, with revolving mixing arms moving in opposite directions. Cf. *mill*. **static ~** A tubular m. with helical elements giving alternating left- and right-hand twists; designed to mix by a fluid's motion.
**mixite** $Cu_2O \cdot As_2O_3 \cdot nH_2O$ with 13% $Bi_2O_3$. An emerald mineral.
**mixture (1)** Substances that are mixed, but not chemically combined **constant boiling ~** A m. of 2 liquids which, at a given pressure, distills unchanged, the boiling point remaining constant. Cf. *azeotropy*. **electrostatic ~** A m. obtained by using electric energy to accelerate conducting particles or ions in a nonconducting medium, and so to impart rapid and violent motion to the dispersed particles. Used to desulfurize fuel oils. **freezing ~** A m. of salts with water or ice which produces low temperatures. **law of ~** Law of *alligation*.
**mixture (2)** Mistura. A pharmaceutical preparation.
**mks system** Meter-kilogram-second system. A technical system of measurements recommended by the International Electrotechnical Commission (1938) as simpler than the cgs system. Subsequently rationalized and expanded to become the internationally used SI system.
**mL*, ml*** Abbreviation for milliliter.
**mm** Abbreviation for millimeter = 1/1,000 m. **$mm^2$** Abbreviation for square millimeter. **$mm^3$** Abbreviation for cubic millimeter.
**mμ** Former symbol for millimicron, $10^{-9}$ m; superseded (SI system) by nm.
**μμ** Former symbol for micromicron, $10^{-12}$ m; superseded (SI system) by pm.
**mmf** Abbreviation for magnetomotive force.
**mmm** Former symbol for millimicron; superseded (SI system) by nm.
**Mn** Symbol for manganese.
**Mo** Symbol for molybdenum.
**m.o., MO** Abbreviation for molecular *orbital*
**mobile** Changing position; moving.
**mobility** (1) The motion of atoms, molecules, ions, or colloidal particles. The mobility, $\alpha$, of an ion in a liquid; $\alpha = 1.037 \times 10^{-5}\lambda t$, where $\lambda$ is the equivalent conductivity, and $t$ the transport number of the ion. (2) The visible motion of colloidal particles and microorganisms Cf. *Brownian motion*.
**mobilometer** A viscometer in which the time is noted for a disk to fall through a column of the liquid under investigation; used for oils and liquid foods.
**mocha** See *coffee*. **m.stone** Moss agate.
**mochyl alcohol** $C_{26}H_{46}O$ = 374.6. An alcohol, m.234, from mochi (Japanese birdlime).
**mock** **m. gold Pyrites**. **m. lead** Sphalerite. **m. ore** Sphalerite. **m. silver** Britannia metal. **m. vermilion** Lead chromate.
**mock-up** A nonworking model of an apparatus or plant intended to show the layout and method of operation
**mode** (1) The actual composition of a substance, e.g., rock, as compared with its norm, q.v. (2) Term. One of three basic control methods used by conventional instrumentation: *proportional control* (corrective action is proportional to the difference between desired and actual values, that is, the error); *reset action* (correction is proportional to both the magnitude and duration of the error); and *derivative action* (correction is proportional to the rate of change of the error). (3) In statistics, the value of highest frequency, corresponding to the peak value of a normal distribution curve.
**Modecate** Trademark for fluphenazine hydrochloride.
**modeccin** A toxin from the passion flower plant
**model** (1) A geometrical arrangement by which an idea or

# EXHIBIT 8

# Remington's PHARMACEUTICAL SCIENCES

A treatise on the theory and practice of pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities and services of the pharmacist as a member of the health team . . . . A textbook and reference work for pharmacists, physicians, and other medical scientists



With the cooperation of more than 300 editors, associate editors, and contributors

*Over 1,000 Illustrations*

**FOURTEENTH EDITION**

1970

*Published in the 150th Anniversary Year*
*of the*
*Philadelphia College of Pharmacy and Science*


MACK PUBLISHING COMPANY
Easton, Pennsylvania 18042

Library of Congress Catalog Card No. 60-53334

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*Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania*

Alcoholic solutions of volatile principles as employed in pharmacy may be regarded as a development of the perfume industry. It was discovered that alcoholic solutions of volatile oils possessed more delicate and fragrant odors than the pure oil itself, and as more aromatic principles were discovered or synthesized, experimentation resulted in the production of innumerable blends to satisfy every individual desire.

The formula and procedure given for Aromatic Ammonia Spirit NF illustrate this method of preparation.

**Aromatic Ammonia Spirit NF**

| | |
|---|---|
| Ammonium Carbonate, in translucent pieces | 34 Gm |
| Strong Ammonia Solution | 36 ml |
| Lemon Oil | 10 ml |
| Lavender Oil | 1 ml |
| Myristica Oil | 1 ml |
| Alcohol | 700 ml |
| Purified Water, a sufficient quantity | |
| To make | 1000 ml |

Dissolve the ammonium carbonate in the strong ammonia solution and 195 ml of purified water by gentle agitation, and allow the solution to stand for 12 hours. Dissolve the oils in the alcohol, contained in a graduated bottle or cylinder, and gradually add the ammonium carbonate solution and enough purified water to make the product measure 1000 ml. Set the mixture aside in a cool place for 24 hours, occasionally agitating it, and then filter, using a covered funnel.

The spirit is a respiratory stimulant and is administered by inhalation of the vapor as required. It is marketed in suitable tight, light-resistant containers but is also available in a single-dose glass vial wrapped in a soft cotton envelope. The vial is easily broken; the cotton acts as a sponge for the spirit.

Ammonium carbonate is a mixture of ammonium bicarbonate and ammonium carbamate ($NH_2COONH_4$). The carbamate reacts with water to form the carbonate.

$$NH_2COONH_4 + H_2O \rightarrow 2NH_4CO_3$$

An ammonium carbonate solution is, therefore, a solution of ammonium bicarbonate and ammonium carbonate in water. However, it decomposes in water, the decomposition products being ammonia, carbon dioxide, and water. The stability of the spirit is improved by the addition of strong ammonia solution. This represses the hydrolysis of ammonium carbonate and, in this way, decreases the loss of dissolved gases.

*Solution with Maceration*—In this procedure, leaves of the drug are macerated in purified water to extract water-soluble matter. They are then expressed, and the moist macerated leaves are added to a prescribed quantity of alcohol. The volatile oil is added to the filtered liquid. Peppermint Spirit NF is made by this process. Peppermint Spirit BPC 1968 differs from the official product in that it is a solution of the volatile oil in alcohol only. The concentration of volatile oil in the final product is about the same but the official preparation possesses a green color. The ready availability of soluble chlorophyll and other coloring agents has led to the frequent suggestion that a more uniform product could be obtained through their use. However, these agents cannot be used in preparing the official article.

The formula and procedure given for Peppermint Spirit NF (page 813) illustrate this method of preparation.

*Chemical Reaction*—No official spirits are prepared by this process. Ethyl nitrite is made by the action of sodium nitrite on a mixture of alcohol and sulfuric acid in the cold. This substance is then used to prepare Ethyl Nitrite Spirit, a product which is no longer official.

*Distillation*—Brandy and Whisky are made by distillation. The latter product is derived from the fermented mash of wholly or partially germinated malted cereal grains and the former from the fermented juice of ripe grapes.

**Incompatibilities**—Spirits are, for the most part, preparations of high alcoholic strength and do not lend themselves well to dilution with aqueous solutions or liquids of low alcoholic content. The addition of such a solution invariably causes a separation of some of the material dissolved in the spirit, the evidence of separation being a turbidity which, in time, may disappear as distinct layering occurs. Salts may be precipitated from their aqueous solutions by the addition of spirits due to their lesser solubility in alcoholic liquids.

Some spirits show incompatibilities peculiar to the ingredients which they contain. For example, Aromatic Ammonia Spirit NF cannot be mixed with aqueous preparations containing alkaloids (eg, codeine phosphate). An acid–base reaction (ammonia–phosphate) occurs and, if the alcoholic content of the final mixture is too low, codeine will precipitate out of solution.

## Sprays

Sprays are solutions of various drugs in oily or aqueous vehicles and are applied to the mucous membrane of the nose and throat by means of an atomizer or nebulizer. The spray device should produce relatively coarse droplets if the action of the drug is to be restricted to the upper respiratory tract. Fine droplets tend to penetrate farther into the respiratory tract than is desirable.

Many of the older sprays contained menthol, thymol, camphor, methyl salicylate, and ephedrine dissolved in light liquid petrolatum. The use of light liquid petrolatum as a vehicle has, however, been severely criticized. There are two basic reasons for this. The first relates to the danger of lipoid pneumonia from the use of these oily preparations. Other reports have indicated that such sprays retard the normal ciliary activity on the nasal mucosa. In addition to this, the basic formulations have been criticized because of the instability of ephedrine in light liquid petrolatum.[15]

On the basis of the above reports, aqueous sprays which are isotonic with nasal secretions and of approximately the same pH are to be preferred. Such sprays may contain antibiotics, antihistamines, vasoconstrictors, alcohol, and suitable solubilizing and wetting agents. The pharmacist will handle many commercial preparations that comply with the basic definition given above and that help to alleviate the nasal congestion due to the common cold. For example, one of these contains chlorpheniramine maleate, phenylephrine hydrochloride, and gramicidin. Another is described as an isotonic, buffered (pH 6.2), aqueous solution containing phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pheniramine maleate, and chlorobutanol. Most of the highly advertised sprays are marketed either in standard dropper bottles or in plastic squeeze units.

Ayerst Laboratories market a throat spray containing anise oil (0.6%), cassia oil (0.1%), pyrilamine maleate (0.05%), antipyrine (0.3%), methyl salicylate (0.05%), menthol (0.1%), sodium caprylate (0.5%), alcohol (1%), glycerol (2%), and methylrosaniline chloride. The "Spray-O-Mizer" squeeze bottles are a

# EXHIBIT 9

WCB# 0034 0376 - 00212281



ORIGINAL

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
CIVIL DIVISION

| | | |
|---|---|---|
| MEDPOINTE HEALTHCARE, INC., | ) | |
| | ) | |
| Plaintiff, | ) | |
| | ) | |
| vs. | ) | CASE NO. |
| | ) | |
| APOTEX, INC., and APOTEX CORP., | ) | 06-164 (SLR) |
| | ) | |
| Defendants. | ) | |
| | ) | |

VIDEOTAPE DEPOSITION OF DR. HOWARD SCHWARTZ
Taken Wednesday, October 17, 2007
From the hour of 9:33 a.m. to 5:21 p.m.
Pages 1 through 264, inclusive
Volume 1
Taken by Counsel for Plaintiff
At
HILTON EL CONQUISTADOR RESORT
Copper Room
10000 North Oracle Road
Tucson, Arizona

Reported by:
CAROL A. McCUE, RMR
Esquire Deposition Services

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